

Carotid Artery Disease:  
Treatment and Associated Risks

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## I Declaration

I, **Dr Jörg Rudolf Ederle** confirm that the work presented in this thesis is my own. It has been carried out at the UCL Institute of Neurology, Queen Square under the supervision of Dr H. Rolf Jäger and Prof Martin M. Brown between April 2006 and December 2011. The work has been presented at national and international conferences and is published in peer-reviewed literature. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

London, December 2011

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I am deeply indebted to him for giving me the chance to be part of his team and for his support and advice in completing this research.

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The work described in this thesis was carried out with the Stroke Research Group at the UCL Institute of Neurology, Queen Square. Adrienne Wallis entered a lot of the data submitted by participating centres into the electronic database. Roland Featherstone managed ICSS and assisted in data extraction. Joanna Dobson provided invaluable advice and help with data analysis. Vanessa Bassan, Estelene Klaasen, Olivia Browne, and Sheree Milloy tirelessly helped with recruitment and follow-up of patients. Helen Tindall kept us all organised. Without their hard work my work would not have been possible and I owe them thanks.

ICSS and CAVATAS are multi-centre trials and the many collaborators, too many to name individually, made ICSS and CAVATAS successful.

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### 3 Abstract

Carotid artery stenosis is a major risk factor of stroke. Carotid endarterectomy is the established treatment of choice for severe carotid stenosis. Carotid stenting has gained widespread acceptance as alternative treatment, although trials of safety and efficacy have been inconclusive and contradictory.

The history of our understanding of stroke and carotid atherosclerotic disease is sketched. Landmark trials of stroke prevention, including the carotid endarterectomy trials are discussed. The long-term results of one of the first trials of endovascular treatment, the Carotid And Vertebral Transluminal Angioplasty Study (CAVATAS) are presented and the results placed in context of other clinical trials of endovascular treatment for carotid stenosis. This Cochrane Review informed the largest completed trial of stenting and surgery in symptomatic carotid stenosis, the International Carotid Stenting Study (ICSS), whose short-term results up to 120 days after treatment are detailed.

Age-related white matter changes are thought to be associated with an increased risk of per-procedural stroke and death. A study investigating the risk of stroke or death associated with age-related white matter changes is presented and discussed.

CAVATAS has suggested that the risks and benefits of endovascular treatment for carotid stenosis may be similar to those of carotid endarterectomy. The Cochrane review revealed variable results of published randomised clinical trials. ICSS showed that carotid stenting was associated with a significantly higher short-term risk of stroke, myocardial infarction or death up to 120 days after treatment than carotid endarterectomy. Age-related white matter changes were shown to increase the risk of stroke or death in both treatment arms.

Carotid endarterectomy should remain the treatment of choice for symptomatic carotid stenosis but stenting remains an option for certain patients, especially those less suitable for carotid endarterectomy. Scope for further research remains to improve patient selection and to compare invasive treatment to modern medical therapy.

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## 6 Abbreviations

|          |   |
|----------|---|
| ACAS     | Asymptomatic Carotid Atherosclerosis Study                                      |
| ACE      | Angiotensin-converting enzyme   |
| ACST     | Asymptomatic Carotid Surgery Trial  |
| ACST-2   | Asymptomatic Carotid Surgery Trial-2  |
| ADC      | Apparent diffusion coefficient  |
| Afx      | Amaurosis fugax   |
| ARWMC    | Age-related white matter changes  |
| BACASS   | Basel carotid artery stenting study   |
| CAPRIE   | Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events              |
| CARESS   | Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis |
| CAS      | Carotid artery stenting   |
| CASANOVA | Carotid Artery Stenosis with Asymptomatic Narrowing: Operation versus Aspirin   |
| CAVATAS  | Carotid And Vertebral Artery Transluminal Angioplasty Study                     |
| CCA      | Common carotid artery   |
| CEA      | Carotid endarterectomy  |
| CEMRA    | Contrast-enhanced magnetic resonance angiography                                |
| CENTRAL  | Central Register of Controlled Trials   |
| CI       | Confidence interval   |
| CONSORT  | Consolidated Standards of Reporting Trials                                      |
| CREST    | Carotid Revascularization Endarterectomy versus Stenting Trial                  |
| CRP      | C-reactive protein  |
| CT       | Computed tomography   |
| CTA      | Computed tomography angiography   |
| DALY     | Disability adjusted life years  |

|        |  |
|--------|--|
| DICOM  | Digital Imaging and Communications in Medicine   |
| DWI    | Diffusion-weighted imaging   |
| ECG    | Electrocardiogram  |
| ECST   | European Carotid Surgery Trial   |
| EDV    | End-diastolic velocity   |
| ESC    | European Society of Cardiology   |
| ESH    | European Society of Hypertension   |
| ESPRIT | European / Australasian Stroke Prevention in Reversible Ischaemia Trial                |
| EVA-3S | Endarterectomy versus angioplasty in patients with symptomatic severe carotid stenosis |
| EVT    | Endovascular treatment   |
| FLAIR  | Fluid-attenuated inversion recovery  |
| GRO    | General Register Office  |
| HR     | Hazard ratio   |
| ICA    | Internal carotid artery  |
| ICSS   | International Carotid Stenting Study   |
| IQR    | Interquartile range  |
| ISRCTN | International Standard Randomised Controlled Trial Number Register                     |
| ITT    | Intention to treat   |
| MACE   | Mayo Asymptomatic Carotid Endarterectomy   |
| MATCH  | Management of Atherothrombosis with Clopidogrel in High-risk Patients                  |
| MCA    | Middle cerebral artery   |
| MI     | Myocardial infarction  |
| MRA    | Magnetic resonance angiography   |
| MRI    | Magnetic resonance imaging   |

|          |  |
|----------|--|
| NASCET   | North American Symptomatic Carotid Endarterectomy Trial  |
| NIHSS    | National Institute of Health Stroke Scale  |
| NINDS    | National Institute of Neurological Disorders and Stroke  |
| OCSF     | Oxfordshire Community Stroke Project   |
| OR       | Odds Ratio   |
| OXVASC   | Oxford Vascular Study  |
| PRoFESS  | Prevention Regimen for Effectively Avoiding Second Strokes   |
| PROGRESS | Perindopril Protection Against Recurrent Stroke Study  |
| PSV      | Peak systolic velocity   |
| PTA      | Percutaneous transluminal angioplasty  |
| PVD      | Peripheral vascular disease  |
| RD       | Risk Difference  |
| SAPPHIRE | Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy               |
| SD       | Standard deviation   |
| SDB      | Stroke Database  |
| SE       | Standard error   |
| SLSR     | South London Stroke Register   |
| SPACE    | Stent-Protected Angioplasty versus Carotid Endarterectomy  |
| SPARCL   | Stroke Prevention by Aggressive Reduction in Cholesterol Levels                                    |
| TCD      | Transcranial Doppler   |
| TESCAS-C | Trial of Endarterectomy versus stenting for treatment of carotid atherosclerotic stenosis in China |
| TIA      | Transient ischaemic attack   |
| TOAST    | Trial of ORG10172 in Acute Stroke  |
| VA       | Veterans Affairs   |
| WHO      | World Health Organisation  |

## 7 Publications Associated with this Thesis

**Ederle, J.** and Brown, M. M. (2006). "The evidence for medicine versus surgery for carotid stenosis." *European Journal of Radiology* **60**(1): 3-7.

Coward, L. J., McCabe, D. J., **Ederle, J.**, Featherstone, R. L., Clifton, A. and Brown, M. M. (2007). "Long-term outcome after angioplasty and stenting for symptomatic vertebral artery stenosis compared with medical treatment in the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomized trial." *Stroke* **38**(5): 1526-30.

**Ederle, J.**, Featherstone, R. L. and Brown, M. M. (2007). "Percutaneous transluminal angioplasty and stenting for carotid artery stenosis." *Cochrane Database Syst Rev*(4): CD000515.

**Ederle, J.** and Brown, M. M. (2008). "Managing carotid stenosis: carotid endarterectomy and stenting." *Minerva Medica* **99**(5): 483-8.

**Ederle, J.** and Brown, M. M. (2008). "Stroke Prevention." *Herz* **33**(7): 518-523.

**Ederle, J.**, Featherstone, R. L. and Brown, M. M. (2008). "A cochrane review of endovascular treatment versus endarterectomy for carotid stenosis." *Journal of Neurology Neurosurgery and Psychiatry* **79**(3): 345-346.

Bonati, L. H., **Ederle, J.**, McCabe, D. J., Dobson, J., Featherstone, R. L., Gaines, P. A., Beard, J. D., Venables, G. S., Markus, H. S., Clifton, A., Sandercock, P. and Brown, M. M. (2009). "Long-term risk of carotid restenosis in patients randomly assigned to endovascular treatment or endarterectomy in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): long-term follow-up of a randomised trial." *Lancet Neurology* **8**(10): 908-917.

**Ederle, J.**, Bonati, L. H., Dobson, J., Featherstone, R. L., Gaines, P. A., Beard, J. D., Venables, G. S., Markus, H. S., Clifton, A., Sandercock, P. and Brown, M. M. (2009). "Endovascular treatment with angioplasty or stenting versus endarterectomy in patients

with carotid artery stenosis in the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS): long-term follow-up of a randomised trial." *Lancet Neurology* **8**(10): 898-907.

**Ederle, J.** and Brown, M. M. (2009). Carotid Stenting: The Evidence Base. Practical Carotid Artery Stenting. Macdonald, S. and Stansby, G. London, Springer: 1-8.

**Ederle, J.,** Featherstone, R. L. and Brown, M. M. (2009). "Randomized controlled trials comparing endarterectomy and endovascular treatment for carotid artery stenosis: a Cochrane systematic review." *Stroke* **40**(4): 1373-80.

**Ederle, J.,** Featherstone, R. L. and Brown, M. M. (2009). "Long-Term Outcome of Endovascular Treatment versus Medical Care for Carotid Artery Stenosis in Patients Not Suitable for Surgery and Randomised in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS)." *Cerebrovascular Diseases* **28**(1): 1-7.

**Ederle, J.,** Dobson, J., Featherstone, R. L., Bonati, L. H., van der Worp, H. B., de Borst, G. J., Lo, T. H., Gaines, P., Dorman, P. J., Macdonald, S., Lyrer, P. A., Hendriks, J. M., McCollum, C., Nederkoorn, P. J. and Brown, M. M. (2010). "Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial." *Lancet* **375**(9719): 985-97.

## 8 Introduction

### 8.1 Purpose and Outline of the Thesis

Carotid artery atherosclerosis, a major risk factor for cerebral ischaemia and stroke is the topic of this thesis. Several competing treatment options developed for patients with carotid artery atherosclerosis have led to uncertainty as to what the safest and most effective way of treating patients with carotid artery disease is and they will be discussed in this thesis. The aim of the thesis is to provide a comprehensive overview of carotid artery atherosclerosis, the available treatment options and how these different treatment modalities compare. The thesis will add to the understanding of management and treatment of carotid artery atherosclerosis.

A brief historical overview of major developments in stroke medicine and carotid artery atherosclerosis in particular will be followed by a definition of stroke and transient ischaemic attack (TIA), which often result from carotid disease. The main questions of pathology (what has happened?) and aetiology (what is the mechanism?) of stroke will be addressed followed by a description of the imaging modalities available to confirm the diagnosis of stroke.

The incidence of carotid artery atherosclerosis as one of the main risk factors of stroke will be discussed. The different techniques of diagnosing and measuring carotid narrowing will be set out and the treatment options carotid endarterectomy, endovascular treatment and medical care will be explained.

This will be followed by a detailed description, analysis and interpretation of two landmark trials of endovascular treatment of carotid artery stenosis. The thesis covers almost two decades of research into carotid artery atherosclerosis starting with the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS). It was one of the earliest and largest trials comparing endovascular treatment to carotid endarterectomy in patients suitable for surgery or medical treatment in patients not



suitable for carotid endarterectomy in a controlled and randomised fashion and spurred further trials on the topic. The International Carotid Stenting Study (ICSS) became the largest randomised clinical trial of endovascular treatment for carotid stenosis and concluded randomisation 16 years after the first patient was randomised into CAVATAS.

After the presentation of these two pivotal trials, they will be put into context of other randomised clinical trials investigating endovascular treatment of carotid stenosis. This will be in the form of a Cochrane-style review, which is the most respected form of reviewing the available evidence of medical interventions or treatments and informs not only treatment decisions but also healthcare policy in general.

The thesis will conclude with a summary discussion of the presented data and an outlook for future research.

## **8.2 Historic Background**

### **8.2.1 First Description of Stroke**

The ancient Greek Hippocratic Corpus contains several references to *apoplexia*, or seizure. “The healthy subject is taken with a sudden pain, he immediately loses his speech and rattles in the throat” (Littré 1839b) can be construed as a clinical description of stroke (Clarke 1963). The Hippocratic Corpus also contains the statement that “unaccustomed attacks of numbness and anaesthesia are signs of impending apoplexy” (Littré 1839a). It has been suggested that this may have been the first description of transient ischaemic attacks.

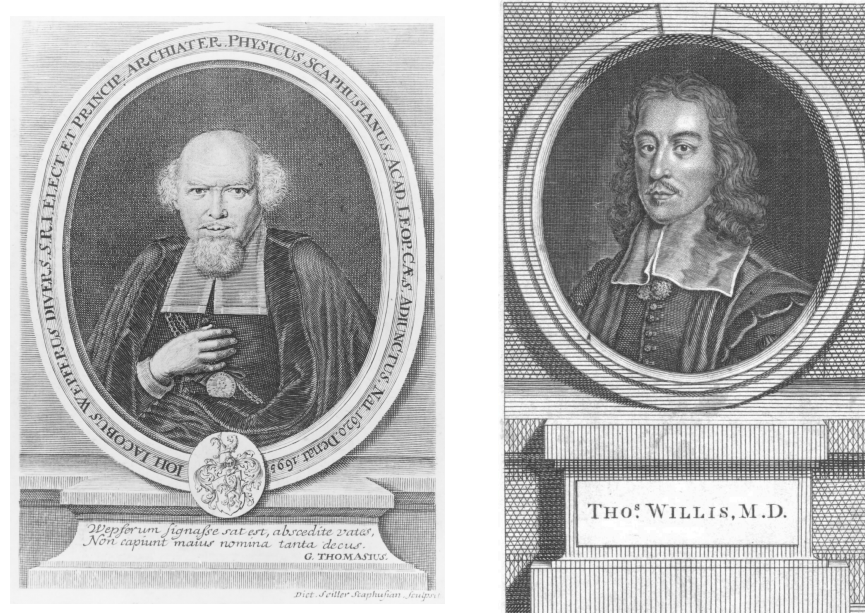
The Greek physicians contributing to the Hippocratic Corpus (5<sup>th</sup> – 4<sup>th</sup> century B.C.) believed that disease was a generalised process. They did not primarily have diagnostic considerations in mind (Clarke 1963).

### **8.2.2 First Description of Carotid Disease**

In the 17<sup>th</sup> century, the Swiss physician Johann Jakob Wepfer (1620 – 1695) and his English colleague Thomas Willis (1621 – 1675), both pictured below in Figure 8.1, greatly

advanced the understanding of cerebrovascular anatomy. Willis provided a graphical representation of the anastomotic network of arteries at the base of the brain that has become known as circle of Willis in his work *De cerebri anatome*. However, it was Wepfer who provided the first written description of these arteries in his work *Historiae apoplecticum* six years before Willis (Gurdjian 1979; Thompson 1996; Tatu *et al.* 2005). It appears that Wepfer was well aware that occlusion of the extra-cranial vessels could lead to “apoplexy”. Willis on the other hand was much more interested in showing that the many anastomoses between carotid and vertebral arteries were able to forestall consequences of carotid occlusion (Gurdjian 1979). Every year the European Stroke Conference honours scientists for their work in the field of stroke with the Johann Jakob Wepfer Award.

Figure 8.1 – Johann Jakob Wepfer (left) and Thomas Willis (right)



Rudolf Virchow (1821 – 1902) described a case of carotid thrombosis and ipsilateral monocular blindness in 1856 and Sir William Richard Gowers (1845 – 1915) described a case of monocular blindness and contralateral hemiplegia in a patient with mitral valve stenosis (Virchow 1856; Gowers 1875). This created the link between clinical presentation and occlusive cerebrovascular disease.

Charles Miller Fisher was one of the first to study clinically diagnosed occlusion of the internal carotid artery at autopsy in the 1950s and began routine removal of the carotid arteries at autopsy. He was able to show that carotid artery disease was responsible for a significant number of strokes (Fisher 2001).

### 8.2.3 First Treatment of Carotid Disease

The first attempted thrombo-endarterectomy reported in an English-language journal is credited to Elliott Hurwitt and his colleagues at Montefiore Hospital in New York City. In January 1953, a 52-year old man was admitted with headache and weakness down his right side of the body with aphasia. Eight days after the admission, an arteriography revealed a left internal carotid artery occlusion. The surgery carried out on the 11<sup>th</sup> day of the hospital admission removed seven centimetres of blood clot from the extracranial portion of the internal carotid artery but failed to remove the intracranial parts of the clot. For fear of dislodging the clot to the brain the vessel was ligated (Strully *et al.* 1953).

On 19 May 1954, Felix Eastcott and colleagues carried out a landmark operation at St Mary's Hospital in London (Eastcott *et al.* 1954). A 66-year old female patient was suffering repeat transient ischaemic attacks lasting around 30 minutes each and was found to have severe carotid stenosis. By the time of the surgery she has had 33 such events over the course of five months. The carotid bifurcation where the stenosis was located was resected and blood-flow restored by end-to-end anastomosis between the common and internal carotid arteries. The patient was completely relieved of her symptoms.

The first case series of carotid endarterectomy was published eleven years after Eastcott's ground-breaking surgery (Debaeky *et al.* 1965). This was the starting point for widespread carotid surgery to correct carotid stenosis. Carotid endarterectomy remained the only available interventional treatment option that could be offered in addition to medical therapy for many years. Its popularity was somewhat dented when two randomised trials raised concerns about the safety of the procedure (Fields *et al.* 1970;

Shaw *et al.* 1984). Subsequently, large trials were undertaken in Europe and North America that eventually restored the reputation of carotid endarterectomy for symptomatic carotid stenosis (Barnett *et al.* 1998; Farrell *et al.* 1998) and to a lesser degree for asymptomatic carotid stenosis (Toole *et al.* 1995; Halliday *et al.* 2004).

#### **8.2.4 First Human Cardiac Catheterisation**

The German physician Werner Forssmann (1904 – 1979) carried out the first human cardiac catheterisation in a daring act of self-experimentation in 1929. He inserted a cannula into his own antecubital vein and passed a 65 cm catheter to the right auricle in the heart. He then walked to the X-ray department to prove the location of the catheter tip (Forssmann 1929). Ferdinand Sauerbruch (1875 – 1951) under whom he started training as a surgical assistant at the Charité in Berlin shortly thereafter did not approve of his work and fired him upon learning of the publication of the article detailing his achievement. The Nobel Foundation in Stockholm, however, recognised Forssmann's important contribution to medicine and in 1956 he was awarded the Nobel Prize for Physiology or Medicine.

#### **8.2.5 The Birth of Interventional Radiology**

On 16 January 1964, Charles Dotter (1920 – 1985) carried out the first percutaneous transluminal angioplasty (PTA). He used a guide wire and coaxial Teflon catheter to dilate the tight, localised stenosis of the superficial femoral artery in a 82-year old woman with leg ischaemia and gangrene who had refused amputation (Dotter *et al.* 1964). To the surprise of the surgical team who had kept the patient in hospital under observation fully expecting the dilated artery to thrombose, the artery stayed open until her death from pneumonia two-and-a-half years later (Rosch *et al.* 2003). This milestone was followed by refinements of the technique and instrumentation in the coming years.

In 1973, the first clinically applicable balloon catheters were introduced (Porstmann 1973). Andreas Grüntzig's polyvinyl chloride balloon catheter was introduced in 1974

(Gruntzig *et al.* 1974) and paved the way to the first coronary artery dilation in 1976 (Gruntzig 1976).

#### **8.2.6 Expandable Stents**

Frustrated with frequently occluding arteries following successful recanalisation, Dotter introduced transluminally placed 'coil spring endarterial tube grafts' in 1969 (Dotter 1969) and they were first approved for use in the biliary system. In the mid 1980s, a variety of self- or balloon-expandable stents made of stainless-steel alloys or Nitinol, an alloy of nickel and titanium were introduced (Rosch *et al.* 2003), among them three self-expandable stainless-steel stents: The Gianturco Z stent, Palmaz stent and Wallstent (Wright *et al.* 1985). Wallstent and Palmaz stents were both used in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) (Brown *et al.* 2001).

#### **8.2.7 Endovascular Treatment of Carotid Disease**

The history of endovascular treatment of carotid stenosis dates back to 1980, when the first percutaneous transluminal angioplasty to treat atherosclerotic stenosis was carried out in a 64-year old man (Mathias 1981). Devices designed to protect the brain from debris dislodged during dilation of the atherosclerotic lesion initially required a double femoral approach (Theron *et al.* 1987). But in 1988, Jacques Theron introduced a new triple coaxial balloon catheter for carotid angioplasty that included a guiding catheter for an occlusive balloon (Theron *et al.* 1990). The first publication from the United Kingdom on transluminal angioplasty for carotid artery stenosis in seven patients was published in 1990 and led directly to the setting up of CAVATAS (Brown *et al.* 1990). The first reports of the use of stents in the carotid artery were published in 1996 (Theron *et al.* 1996; Yadav *et al.* 1996). Nevertheless, The American Heart Association counselled against the widespread use of carotid angioplasty and stenting without evidence from randomised trials, citing CAVATAS as the only multicentre clinical trial underway at the time (Bettmann *et al.* 1998).

## 8.3 Stroke and Transient Ischaemic Attack

### 8.3.1 Definition of Stroke and Transient Ischaemic Attack

According to the World Health Organisation (WHO) stroke is defined as rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer, or leading to death, with no apparent cause other than of vascular origin (Hatano 1976).

This is a fairly broad definition of stroke as a clinical syndrome. While it stipulates that the onset of symptoms should be rapid and their duration 24 hours or more (or leading to death), it offers no further description of the nature of cerebral dysfunction and underlying vascular pathology.

The blood supply to the brain can be adversely affected by virtually any disease that affects the blood, the heart or the blood vessels themselves. The nature and location of underlying pathology will determine the clinical pattern and severity of cerebral dysfunction.

Symptoms lasting less than 24 hours but fulfilling all other of the above criteria have been excluded from the above definition. They are defined as transient ischaemic attacks (TIA). While the chosen minimum duration for stroke for the above definition was somewhat arbitrary, TIAs in practice last for a few minutes only in most cases (Brown *et al.* 2006). However, waiting for 24 hours before making the diagnosis of stroke cannot be regarded as a viable option, given that no time should be wasted in the acute treatment of stroke, a fact that is used to promote stroke awareness in the catchphrase “time is brain”. Studies of MRI in patients with transient ischaemic attacks have demonstrated that up to 50% of patients with the classically defined transient ischaemic attack show abnormalities on diffusion-weighted MR imaging (DWI) (Engelter *et al.* 1999; Kidwell *et al.* 1999). Classically defined TIA with DWI abnormalities was also associated with an increased risk of subsequent stroke (Purroy *et al.* 2004; Prabhakaran *et al.* 2007). It has therefore been suggested to move away from a definition of TIA based on duration of symptoms

alone. The American Heart Association has endorsed a revised definition of TIA that uses tissue as criterion: A transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction (Easton *et al.* 2009). It could be argued against this definition that the required brain imaging will vary greatly depending on available resources, particularly on the availability of 24-hour MRI. If this tissue-based definition of TIA was used in research, epidemiological studies carried out in a community setting may be more difficult to conduct since MRI to confirm the diagnosis will not always be available.

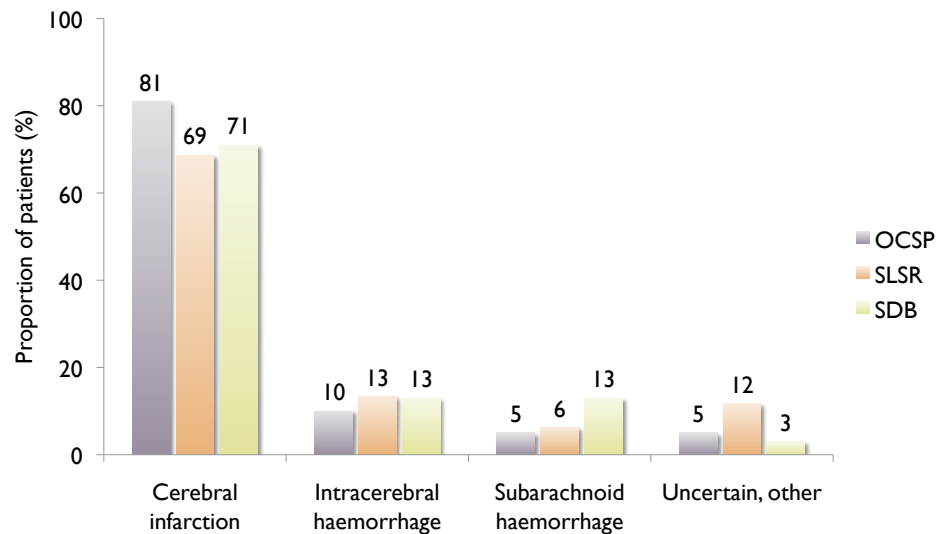
### 8.3.2 Pathogenesis of Stroke and TIA

In order to determine the appropriate management and treatment of stroke patients, the underlying pathogenic mechanisms need to be elucidated. They can be broadly divided into two categories: (1) Cerebral infarction and (2) haemorrhage. The latter can further be divided into (a) intracerebral and (b) extracerebral (but intracranial) haemorrhage (subarachnoid, subdural, epidural haemorrhage).

Cerebral infarction accounted for 81%, intracerebral haemorrhage for 10% and subarachnoid haemorrhage for 5% of all strokes in the Oxfordshire Community Stroke Project (Bamford *et al.* 1990). In roughly 5% of patients, the mechanism of stroke remained uncertain, largely because these patients were elderly and frail and the investigators had refrained from transporting them to hospital to perform a CT of the brain (Figure 8.2).

**Figure 8.2 – Distribution of stroke by diagnosis subtype**

The distribution of stroke in the Oxfordshire Community Stroke Project (OCSP,  $n = 657$  patients), South London Stroke Register (SLSR,  $n = 1,254$ ), and the NINDS Stroke Database (SDB,  $n = 1,805$ ). Numbers are percentages.



The South London Stroke Register found slightly different proportions with 69% of strokes being confirmed radiologically as infarction, 13% intracerebral haemorrhage, and 6% subarachnoid haemorrhage (Wolfe *et al.* 2002). This may reflect differences in demography and racial mix in a mostly rural (Oxfordshire) *versus* city (South London) setting. The South London Stroke Register findings were similar to the distribution of stroke subtype in the NINDS Stroke Data Bank (Foulkes *et al.* 1988).

A TIA is presumed to be ischaemic rather than haemorrhagic in nature (Brown *et al.* 2006), although a small proportion of about 2% of TIAs demonstrate a small intracerebral haemorrhage on imaging.

### 8.3.3 Aetiology of Cerebral Infarction and TIA

Most strokes and transient ischaemic attacks are caused by thrombo-embolism from either the heart (cardio-embolic), atherosclerosis in a large extracranial or intracranial vessel (atherothrombotic), or disease of the small perforating vessels in the brain (lacunar stroke). Rare causes of ischaemic stroke such as sickle cell disease, dissection, or atrial



myxoma may be identified, but in a large proportion of patients the origin of infarction or TIA remains elusive or more than one cause can be identified (Figure 8.3).

A uniform system of classifying ischaemic stroke type has been developed for use in the Trial of ORG 10172 in Acute Stroke (TOAST) (Adams *et al.* 1993). The TOAST classification has gained widespread acceptance in clinical practice. It divides stroke into 5 categories:

- (1) Large-vessel atherosclerosis
- (2) Cardio-embolic small-vessel occlusion
- (3) Small-vessel occlusion (lacune)
- (4) Other determined cause
- (5) Undetermined aetiology

The TOAST classification defines lacunar strokes as a clinical syndrome and emphasises size of the infarct. This may lead to a small deep infarct due to middle cerebral artery atherosclerosis falsely being classified as small-vessel occlusion. Stroke of undetermined aetiology is a very inhomogeneous group in the TOAST classification. It groups patients with at least two different causes with those patients in whom work-up did not reveal a cause of stroke as well as patients with mild carotid artery stenosis (< 50%) (Amarenco *et al.* 2009a). This not only has implications for research, where it may lead to inappropriate patient selection but also may impact on clinical care. Grouping these patients together in the category of undetermined aetiology may lead to an over-sizing of this group and result in inappropriate closure of innocent patent foramen ovale (Amarenco *et al.* 2009a).

A new stroke classification taking into account that many patients display more than one risk factor has since been proposed. The A-S-C-O classification grades patients in the categories atherosclerosis (A), small vessel disease (S), cardioembolic (C) and other cause (O) from 1 ('definitely a potential cause of the stroke') to 3 ('unlikely a direct cause of the index stroke, but disease present') (Amarenco *et al.* 2009b). This classification provides a more complete picture of a patient's likely underlying cause of stroke. It is not very

useful in the clinical setting and might be more useful in research where a as precise description and categorisation of stroke as possible is required.

### **Large-vessel Atherosclerosis**

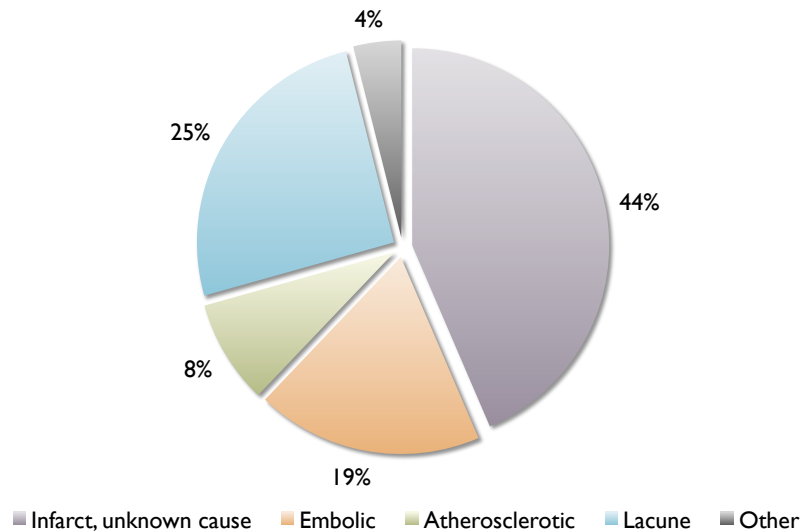
Large-vessel atherosclerosis is largely associated with stenosis either of the internal carotid artery itself or at the site of the carotid bifurcation. Less frequently it is due to stenosis of the large intracerebral arteries.

Large-vessel atherosclerosis accounts for about 6% of all strokes (Foulkes *et al.* 1988). However, this seems to be an underestimate since 6% was the proportion of stenosis greater than 70% where the association with stroke was clear. Up to 40% of cases have some degree of carotid atherosclerosis that may have been responsible for the symptoms and the proportion of stroke attributed to large-vessel atherosclerosis varies according to the criteria used for making the diagnosis.

It is thought that rupture of atherosclerotic plaque leads to platelet aggregation at the site of rupture and thrombus formation. This can either lead to local occlusion or embolisation to a distal vessel (Rothwell 2007). Several studies in recent years have investigated the link between ruptured atherosclerotic lesions (unstable plaque) and cerebral infarction and found a correlation between characteristics of plaque instability and recent symptoms, particularly stroke (Clarke *et al.* 2003; Spagnoli *et al.* 2004; Redgrave *et al.* 2006).

**Figure 8.3 – NINDS Stroke Database: Distribution of ischaemic stroke by subtype**

Shown is the proportion of patients (%;  $n = 1,305$ ) in each category enrolled in the NINDS Stroke Database (Foulkes *et al.* 1988).



Large-vessel stenosis or occlusion may remain asymptomatic if sufficient collateral circulation (likely to be congenital) via the external carotid artery or the circle of Willis is present (Powers 1991; van Everdingen *et al.* 1998; Liebeskind 2003) and unpublished observations suggest that up to 90% of carotid occlusions are asymptomatic. The collateral circulation is not always adequate to maintain sufficient blood flow to the brain. This haemodynamic failure may lead to ischaemia (Grubb *et al.* 1998; Derdeyn *et al.* 2007).

### Cardio-embolism

Patients with arterial occlusions attributed to an embolus arising from the heart fall into this category (Adams *et al.* 1993). Atrial fibrillation, recent myocardial infarction, mechanical prosthetic heart valve and infective endocarditis are among the high-risk sources of cardiac emboli. Cardio-embolism accounts for about 20% of ischaemic strokes (Foulkes *et al.* 1988).

### Small-vessel Occlusion

Occlusion of small penetrating branches of the cerebral arteries leads to infarction of deep white matter regions of the cerebrum or brainstem and grey matter in the basal ganglia. These infarcts are often small in size depending on the size of the affected artery. Their name is derived from the Latin word *lacuna* (hole) and is a reference to their pathological appearance as fluid-filled cavities (Dechambre 1838; Fisher 1965).

Depending on the size of the affected penetrating artery, different pathological mechanisms are incriminated in the formation of lacunar infarcts. Lipohyalinosis associated with fibrinoid necrosis and infiltration of the vessel wall by macrophages leads to occlusion of very small arteries (40 to 200  $\mu\text{m}$  in diameter) (Fisher 1982).

Intracranial atherosclerosis of the proximal portion of the perforating artery (microatheroma), the parent vessel (mural atheroma) or at the origin from the parent vessel (junctional atheroma) affects vessels in the range of 200 to 900  $\mu\text{m}$  in diameter and leads to larger infarcts (Lammie 2000). Radiologically, lacunar infarcts are defined as discrete areas of decreased attenuation on CT or abnormal signal intensity on MRI of less than 1.5 cm in diameter located in the basal ganglia, internal capsule, thalamus, brainstem or corona radiata (Brown *et al.* 1988).

Charles Miller Fisher was able to connect his pathological findings to several clinical syndromes (Fisher 1965) and he described 5 classical clinical syndromes:

- **Pure motor hemiparesis** is defined as palsy of the face, arm, leg on one side without accompanying sensory disturbances, alterations of the visual field, or aphasia (Fisher *et al.* 1965)
- **Pure sensory stroke** is characterised by hypoaesthesia and/or paraesthesia
- **Sensory motor stroke** combines features of the pure motor and pure sensory stroke syndromes
- Hemiparesis in association with homolateral “cerebellar” signs characterises the **ataxic hemiparesis** and **dysarthria-clumsy-hand syndromes**.

### Other Determined Causes of Stroke

The list of causes of stroke that do not fall into one of the above categories is vast. These only account for 3% of all strokes (Foulkes *et al.* 1988) but often require specific treatment. They are especially important to consider in young patients in whom the conventional risk factors for stroke such as hypertension, atrial fibrillation and atherosclerosis are less prevalent. In many cases the rare causes are systemic diseases and stroke are only one of many possible manifestations.

#### 8.3.4 Epidemiology

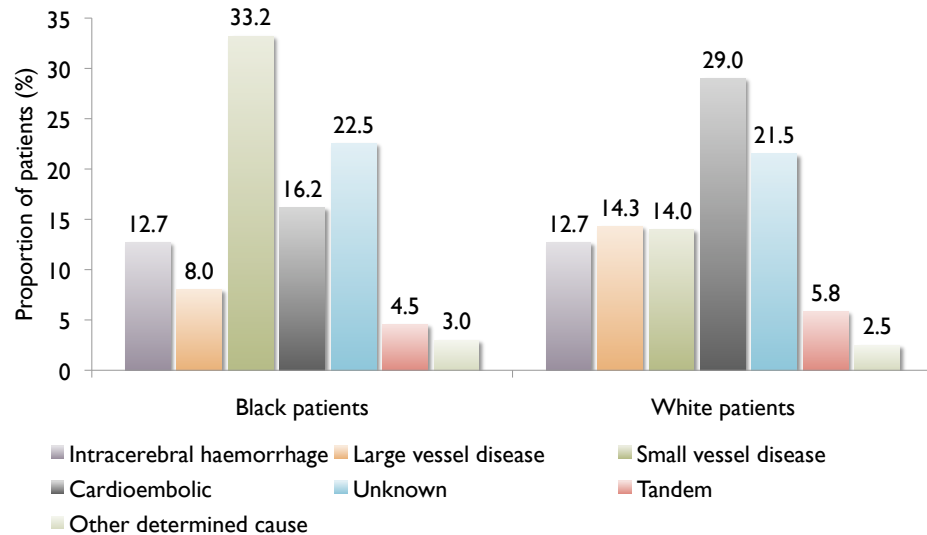
Stroke is one of the leading causes of death and adult disability. In 2001, almost 10% of total deaths worldwide were due to cerebrovascular disease (Lopez *et al.* 2006). In high-income countries, cerebrovascular disease was the second most common cause of disease burden and it was among the top five causes of disease burden in low-to-middle-income countries as measured by disability adjusted life years (DALY) (Lopez *et al.* 2006).

The majority of strokes occur in the age group of over 65 years (Bamford *et al.* 1990; Rothwell *et al.* 2004a) but can occur at any age from birth onwards. A quarter of strokes occur under the age of 65. Overall, around 30% of patients will have died after a stroke and a further one-third of patients will be dependant on others (Bamford *et al.* 1990).

Population-based studies have found incidences of first stroke per 1,000 population of 1.33 in a multi-ethnic community in South London, 1.45 in Oxfordshire and 1.58 in East Lancashire (Du *et al.* 1997; Wolfe *et al.* 2002; Rothwell *et al.* 2004a). Differences between subgroups have been described with respect to different stroke subtypes (Figure 8.4). In South London, cardioembolic stroke was more frequent in White patients than in Black African or Black Caribbean patients, while small-vessel disease and intracerebral haemorrhage were more common in Black African patients (Markus *et al.* 2007).

**Figure 8.4 – Distribution of stroke (ischaemic and haemorrhagic) by TOAST criteria**

Shown are the proportions of Black ( $n = 600$ ) and White patients ( $n = 600$ ) with stroke in the South London Ethnicity and Stroke Study (Markus *et al.* 2007). Numbers are percentages.

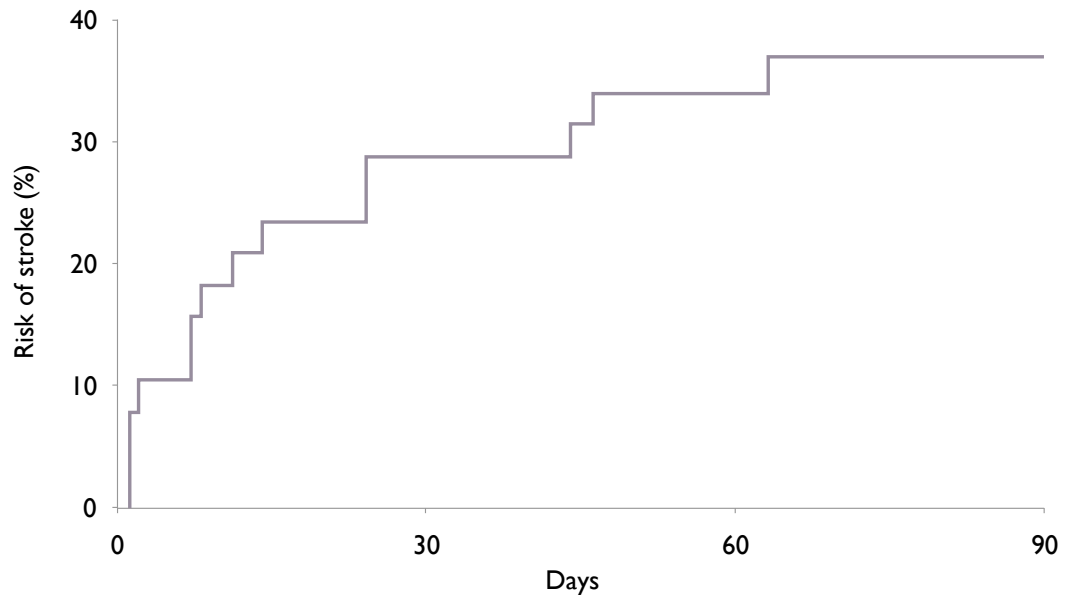


The rate of recurrent stroke is high. A population-based study carried out in Southern Germany found recurrent stroke in 24% of patients over a period of 5 years (Kolominsky-Rabas *et al.* 2006). Patients with symptomatic carotid stenosis are at an especially high-risk of recurrent stroke. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the risk of fatal or nonfatal ipsilateral stroke was 22.2% over five years in patients treated medically and 15.7% in patients treated surgically (Barnett *et al.* 1998). Many patients never got into NASCET because of early recurrence and the true rate of recurrent stroke in patients with previously symptomatic carotid artery stenosis is undoubtedly higher than reported in NASCET.

The Oxford Vascular Study (OXVASC) included 38 patients with carotid stenosis greater than 50% (Figure 8.5). The risk of recurrent stroke prior to any endarterectomy in these patients was 24% at 14 days and 37% at 12 weeks (Fairhead *et al.* 2005).

**Figure 8.5 – Oxford Vascular Study: Risk of recurrent stroke**

Shown is the risk in 38 patients with TIA or non-disabling stroke with  $\geq 50\%$  carotid stenosis up to the day of any endarterectomy. Adopted from (Fairhead *et al.* 2005) with permission from Wolters Kluwer Health.



In asymptomatic carotid stenosis the risk of stroke is lower, with 9.5% of patients suffering a stroke in the carotid territory over a 5-year period (Halliday *et al.* 2004). However, medical treatment at the time the surgical trials were carried out differed from today's clinical practice. Especially lipid-lowering medication was used only in a minority of patients (Barnett *et al.* 1998).

The cost of stroke to society is considerable. In the UK, direct stroke costs account for about 5.5% of National Health Service expenditure, or £ 4 billion (Saka *et al.* 2009). In Germany, the direct costs of stroke amount to € 2.5 billion (Statistisches Bundesamt 2007).

## 8.4 Imaging the Brain

Structural brain imaging is vital in correctly diagnosing cerebral infarction and differentiating it from haemorrhage and other pathological processes that may mimic stroke and guides further investigations and treatment. The mainstay imaging technique is x-ray computed tomography (CT) because of the speed of study acquisition and wide

availability of CT scanners. It is the diagnostic imaging modality of choice to exclude intracerebral haemorrhage. Magnetic resonance imaging (MRI) has a number of advantages but is more expensive, time consuming, and not yet as widely available.

#### **8.4.1 X-ray Computed Tomography**

Very early changes of cerebral infarction may be very subtle and difficult to pick up on x-ray computed tomography (CT). The major early signs of infarction in the territory of the middle cerebral artery (MCA) involve blurring of the internal capsule, loss of distinction of the insular ribbon, loss of grey and white matter differentiation and effacement of the sulci. They can be identified within the first few hours of a stroke (Beauchamp *et al.* 1999). Acute thrombosis or embolic occlusion of a major vessel may be indicated by a hyper-dense appearance of the affected vessel.

Ischaemia leads to cerebral capillary dysfunction and water influx into the brain (Simard *et al.* 2007). Over the next 24 hours, these changes evolve into the clearly defined hypodense appearance of established infarction (Figure 8.6).

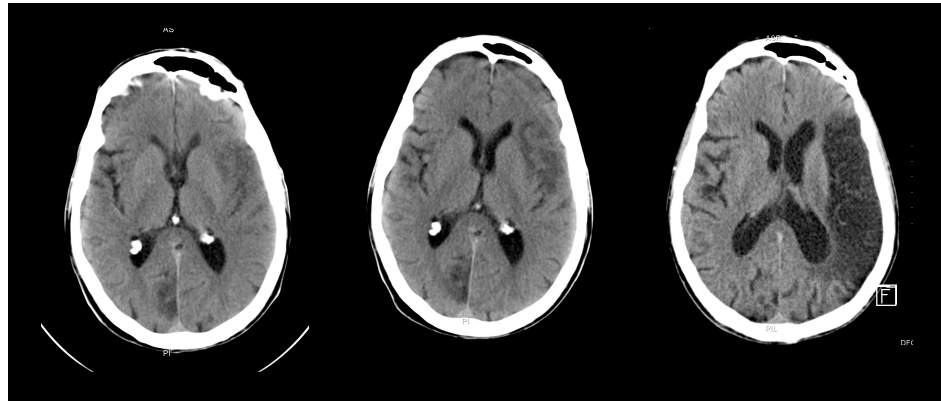
The Alberta Stroke Project early CT score (ASPECTS) divides the middle cerebral artery territory into ten regions that are scored for the presence or absence of ischaemic changes. This score was shown to predict poor outcome following thrombolysis (Barber *et al.* 2000). The appearance of ischaemic changes evolve over the next few weeks and infarcted tissue becomes increasingly hypodense. However, CT may be normal within the first 24 hours if the infarct is small and acute small white matter infarcts may be very difficult to diagnose in the presence of leukoaraiosis.

The high contrast between bone and brain parenchyma in the posterior cerebral fossa often causes severe beam-hardening artefacts that make the assessment of the brainstem and cerebellum difficult (Merino *et al.* 2010).



**Figure 8.6 – X-ray computed tomography of ischaemic stroke**

Serial CT images of a left MCA territory stroke in a 71-year old female patient. The infarct is already well demarcated on the day of stroke onset (left) and 3 days after the event (middle). However, both studies underestimated the true area of damage visible after 10 months (right). Images courtesy R. Jäger



Haemorrhage usually leads within minutes to an increase in density (Figure 8.7). Over time the imaging appearance of haemorrhage changes and an area of haemorrhage will appear less dense. In delayed CT it is often impossible to distinguish between infarction and haemorrhage. This phenomenon has been reported to occur by 14 days for lesions of moderate size (Dennis *et al.* 1987). Haemorrhagic lesions smaller than 20 mm in diameter were reported to be iso-dense in 25% of cases within 9 days of stroke (Wardlaw *et al.* 2004).

**Figure 8.7 – X-ray computed tomography of acute intracerebral haemorrhage**

Shown is a CT and CT angiography of an acute intracerebral bleed (left and middle) in a patient with underlying arterio-venous malformation (right, arrow). Images courtesy R. Jäger.



Perfusion CT measures brain haemodynamics by tracking a bolus of *i.v.* contrast and can identify areas of hypoperfusion in the setting of acute stroke (Hoffmann *et al.* 2012).

Cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit time (MTT) can be calculated. Their relationship is described by  $CBF = CBV / MTT$ , known as the central volume principle (Muizelaar *et al.* 1997).

In stroke patients, perfusion CT aims at distinguishing unsalvageable tissue (infarct core) from tissue that may either die or survive, depending on whether timely reperfusion occurs (penumbra). In the infarct core the perfusion pressure is reduced to such extent, that autoregulation fails, resulting in reduced CBF and CBV.

In the penumbra, autoregulation is preserved and induces capillary dilatation in an attempt to maintain adequate circulation. This preserves or increases CBV in the face of reduced CBF. Mean transit time is reduced in the infarct core due to decreased perfusion pressure (Hoffmann *et al.* 2012). The exact parameters and thresholds that best characterise the infarct core and penumbra are yet to be defined (Dani *et al.* 2011).

CT angiographic source data provide a qualitative picture of cerebral blood flow and has been shown to be superior to non-enhanced brain CT in detecting early changes of cerebral ischaemia and in predicting the final extent of the infarct (Ezzeddine *et al.* 2002; Schramm *et al.* 2002; Camargo *et al.* 2007).

A multimodal acute stroke CT protocol should include unenhanced CT, perfusion CT and CT angiography.

#### **8.4.2 Magnetic Resonance Imaging**

Early changes of cerebral infarction are more easily picked up by magnetic resonance imaging (MRI) with an overall sensitivity within 6 hours of stroke onset in the region of 90% (Schellinger *et al.* 2010). After a few hours the signal intensity increases on T2-weighted and decreases on T1-weighted images. Several special MRI sequences have been developed that increase the diagnostic yield compared to CT (Fiebach *et al.* 2002).

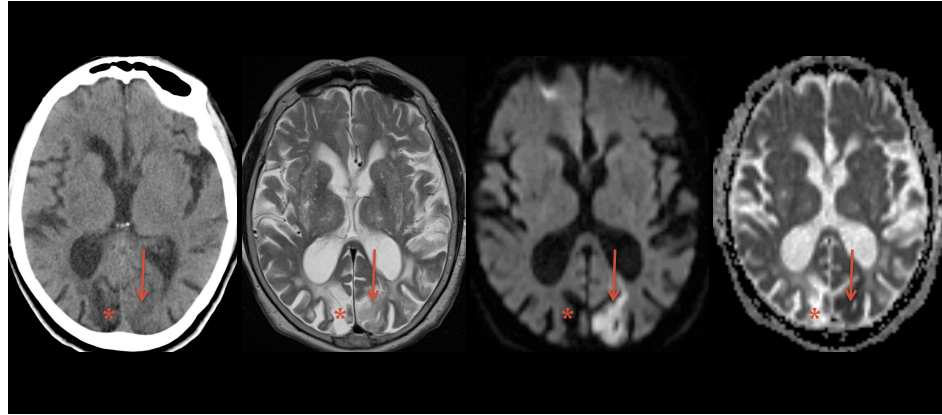
Diffusion-weighted imaging (DWI) measures the random Brownian motion of water molecules due to thermal energy (Hoffmann *et al.* 2012). Brain ischaemia causes a

shortage of metabolites and results in membrane dysfunction and cytotoxic oedema. The movement of water from the extracellular into the intracellular space in turn leads to a narrowing of the extracellular matrix and restriction of molecular movement in the extracellular space. After only a few minutes, ischaemic lesions become apparent on DWI as hyperintense signal (Hjort *et al.* 2005). Serial diffusion weighted imaging demonstrated that in non-treated patients DWI lesions grow in size over hours and days (Schwamm *et al.* 1998). There has been debate whether DWI lesions represent the infarct core and therefore irreversible tissue damage. Although a small proportion of DWI lesions may be reversible, particularly after intra-arterial recanalisation, this reversal is often only temporary (Kidwell *et al.* 2000; Kidwell *et al.* 2002). Recent data suggest that presence of diffusion restriction can be taken as a clinically reliable indicator of irreversible ischaemic damage (Campbell *et al.* 2012).

Established infarcts exhibit an increase in signal intensity on T2-weighted images and may appear bright on DWI (T2 shine-through). DWI should therefore always be interpreted together with the apparent diffusion coefficient (ADC) maps, which measure the change in diffusion more directly. On ADC maps, acute infarction appears as a reduction in signal and thus allows distinguishing acute from established infarction (Figure 8.9 and Figure 8.8). Over the next few days, a pseudo-normalization of ADC values takes place before they finally increase.

**Figure 8.8 – CT and MRI of acute and chronic ischaemic stroke**

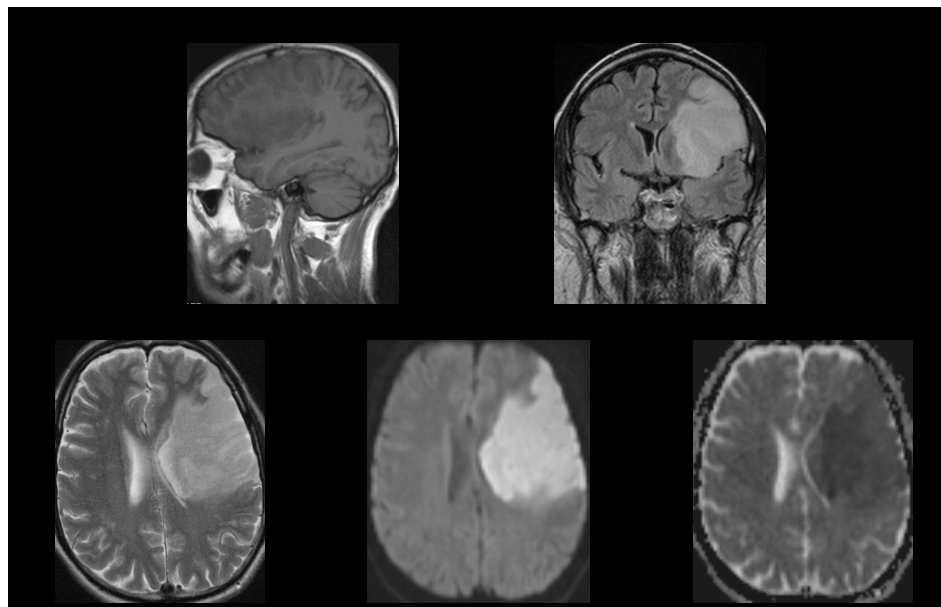
Shown are a CT, T2w-MRI, DWI and ADC (from left to right) in a patient with a chronic right-sided (\*) and acute left-sided occipital infarct (arrow). Images courtesy R. Jäger.



Gradient-recalled echo MRI can accurately exclude intracerebral haemorrhage (Fiebach *et al.* 2004). The paramagnetic properties of degraded blood products (deoxyhaemoglobin) allow their visualisation on MRI in the acute phase as focal hypointensities (Hoffmann *et al.* 2012).

**Figure 8.9 – MRI of an acute left MCA territory stroke**

Shown are sagittal T1w, coronal FLAIR (top, left to right), and transverse T2w, DWI, and ADC (bottom, left to right) sequences of an acute left MCA territory stroke. Images courtesy R. Jäger.



T2-weighted fluid-attenuated inversion recovery sequences (FLAIR) visualise white matter and small cortical lesions particularly well due to the suppression of free water signal (Beauchamp *et al.* 1999). Changes in FLAIR signal intensities are dependent on time since symptom onset and were shown to be useful as surrogate marker of stroke age (Petkova *et al.* 2010). Ischaemic changes are not visible on FLAIR within 6 hours of stroke onset (Merino *et al.* 2010). Combining DWI and FLAIR has shown to be helpful in timing stroke onset. Positive findings on DWI and absence of hyperintensity on FLAIR indicate that the stroke has occurred less than 4.5 hours previously (Thomalla *et al.* 2011).

Unwitnessed stroke accounts for more than 20% of all strokes (Maas *et al.* 2011). Studies are under way investigating the combination of DWI and FLAIR and may in the future allow extending thrombolysis to patients who are currently not eligible for thrombolytic treatment because of the unknown time of onset of stroke (Thomalla *et al.* 2011).

Vessel hyperintensities detected by FLAIR indicate disordered blood flow from collateral vessels distal to the arterial occlusion or stenosis and is an indicator for tissue at risk for infarction but does not predict response to thrombolysis (Schellinger *et al.* 2005; Azizyan *et al.* 2010).

Similar to CT, MR can be used to generate perfusion imaging. Two methods are available. Arterial spin-labelling relies on the detection of magnetically labelled water protons to measure perfusion. Arterial protons are labelled by applying radiofrequency pulses upstream from the imaging plane. Once labelled blood reaches the imaging section, images are obtained in the labelled and unlabelled state. Perfusion parameters are obtained by subtracting the two imaging sets (Pollock *et al.* 2009; Hoffmann *et al.* 2012). The technique is still at an experimental stage but does not require intravenous gadolinium-based contrast agents, which is needed in dynamic susceptibility contrast-enhanced imaging (DSC-PWI).

DSC-PWI measures the decrease in T2-signal caused by the susceptibility effect of intravascular MR contrast agents. The signal changes during the first pass through the

capillary bed are tracked to create time-intensity curves used to calculate the perfusion parameters CBF, CBV and MTT. This step is more complicated as is the case in perfusion CT because the relationship between signal intensity and gadolinium concentration is not linear. The ideal criteria to describe the infarcted area are yet to be defined (Kane *et al.* 2007).

In combination with DWI, perfusion imaging can be used to estimate the ischaemic penumbra, with the DWI lesion representing the infarct core and the PWI lesion representing the complete hypoperfused area including the potentially salvageable penumbra.

The major disadvantages of MRI are its high cost, duration of study acquisition and the fact that a number of patients with metal implants may be excluded. MRI may also be difficult to carry out in claustrophobic patients.

A clinical multimodal stroke MRI protocol should include DWI/ ADC, gradient-echo, FLAIR, MR angiography and perfusion-weighted imaging.

## **8.5 Internal Carotid Artery Stenosis**

### **8.5.1 Incidence of Carotid Artery Stenosis**

Information on the prevalence of carotid stenosis is only available for select patient populations. In a study of 526 subjects the prevalence of stenosis greater than 50% was 6.1% in men aged 75 years or older (Josse *et al.* 1987). In a different study of predominantly male patients treated for non-vascular diseases, the prevalence of asymptomatic carotid stenosis was 6.5% (Fowl *et al.* 1991). A systematic review of published literature showed a prevalence of moderate (more than 50%) stenosis of 4.2% (de Weerd *et al.* 2009).

### **8.5.2 Carotid Artery Stenosis and the Risk of Stroke**

Carotid stenosis is well recognised as a major risk for stroke. A study of the natural history of asymptomatic patients with extracranial artery disease, the majority of which

were carotid stenoses, showed an annual stroke morbidity of 0.4% (Hennerici *et al.* 1987). An analysis carried out in the European Carotid Surgery Trial (ECST) population showed a 2.1% overall risk at 3 years of stroke lasting more than 7 days in the territory of mild to moderate (0 – 69%) asymptomatic carotid artery stenosis but the risk increased to 9.8% in patients with stenosis greater than 80% (Rothwell *et al.* 1995). More recently, the annual risk of stroke in patients with asymptomatic stenosis greater than 50% was found to be 0.34% for any ipsilateral ischaemic stroke (Marquardt *et al.* 2010) and 1.0% for any ipsilateral carotid hemispheric stroke in patients with greater than 60% carotid artery stenosis (Abbott *et al.* 2005). This reduction in annual risk is likely to be at least in part due to improved medical therapy, particularly cholesterol and blood pressure control.

The Asymptomatic Carotid Surgery Trial (ACST) reported a 11.0% 5-year risk of stroke in patients allocated deferred surgery, with half of the strokes (62 in 1560 patients) occurring in the territory of the ipsilateral carotid artery (Halliday *et al.* 2004). But this may overestimate the risk in the population as a whole because of selection bias. Many of the patients may also have had previous symptoms from coronary, peripheral or contralateral carotid stenosis.

### 8.5.3 Imaging the Carotid Artery

Before the impact and consequences of carotid artery stenosis can be discussed further it is important to appreciate how the diagnosis of carotid stenosis is made and how the techniques used to measure the degree of narrowing differ.

Several invasive and non-invasive radiological investigations that allow the degree of narrowing to be estimated from the images have emerged over time. Catheter angiography has been established for years as the method of choice in the diagnosis of carotid stenosis. Ultrasound, CT angiography (CTA) and MR angiography with (CEMRA) or without contrast agent (MRA) are less invasive imaging modalities. A combination of non-invasive techniques is recommended today to detect carotid stenosis.

Figure 8.10 shows an example of a carotid artery stenosis on conventional angiography and CTA.

**Figure 8.10 – Conventional and CT angiography of carotid stenosis**

*Shown is a left carotid artery stenosis on angiography and corresponding CTA. Images courtesy R. Jäger.*



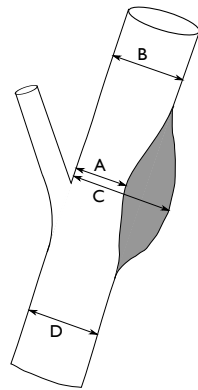
### Catheter Angiography

For many years, catheter angiography was the first-line investigation of carotid stenosis. Both the European and North American surgery trials of symptomatic carotid stenosis required catheter angiography at baseline. However, diagnostic angiography in itself carries a risk of neurological complications reported in around 1% of patients (Willinsky *et al.* 2003). It has therefore been largely replaced by non-invasive imaging modalities as first choice diagnostic technique and is only used in therapeutic indications or if non-invasive imaging is inconclusive (Hoffmann *et al.* 2012).

### The NASCET Method of Measuring Carotid Stenosis

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) used different methods to measure carotid stenosis on angiography. Figure 8.11 illustrates where measurements of the carotid artery are taken on angiograms for calculating the degree of carotid stenosis.





**Figure 8.11 – Diagram of three methods of measuring carotid stenosis on angiogram.**

The diagram illustrates where measurements for equations (1), (2) and (4) are taken.

A, B and D are measurements made on a visible column of x-ray contrast; C is a visual estimate of the likely normal lumen diameter before the development of the stenosis.

NASCET measured stenosis as a fraction of the minimum luminal diameter and the diameter of the distal internal carotid artery:

$$\text{Degree of stenosis (\%)} = \frac{B - A}{B} \times 100 \quad (1)$$

In near occlusions with collapse of the distal carotid artery this method underestimates stenosis, but the correct application of the method arbitrarily assigns a stenosis of 95% to cases where there is distal collapse.

The ECST Method of Measuring Carotid Stenosis

The ECST method requires an estimate of the diameter of the “original”, disease-free carotid bulb:

$$\text{Degree of stenosis (\%)} = \frac{C - A}{C} \times 100 \quad (2)$$

It is important to be clear which method was used to measure stenosis, because the ECST method results in a higher degree of apparent stenosis than the NASCET method (Rothwell et al. 2003). NASCET is the most widely used method and NASCET measurements may be converted into ECST stenosis by the following formula (Rothwell et al. 1994a):

$$\text{ECST of \% stenosis} = \frac{6}{10} \times \text{NASCET \% stenosis} + 40 \quad (3)$$

### The Common Carotid (CC) Method of Measuring Carotid Stenosis

This third method of measuring of carotid stenosis has also been used in research (Brown *et al.* 2001) and incorporates the diameter of the common carotid artery as the denominator:

$$\text{Degree of stenosis (\%)} = \frac{D - A}{D} \times 100 \quad (4)$$

This method has the advantage of being easy to use and having a lower intra- and inter-observer variability than the NASCET and ECST methods (Rothwell *et al.* 1994b). The results of the common carotid method are very similar to ECST measurements and equation (5) may be used to convert NASCET measurements into CC degree of stenosis analogous to equation (3):

$$\text{CC of \% stenosis} = \frac{6}{10} \times \text{NASCET \% stenosis} + 40 \quad (5)$$

### Comparison of the Different Grading Methods

As laid out above each method of grading carotid stenosis takes a different approach. A study comparing the NASCET, ECST and CC grading methods in 86 patients made several interesting observations (Staikov *et al.* 2000).

Generally, the inter-observer agreement was good for all three methods. The Common Carotid method appeared to be the most reproducible with 66% of measurements showing an inter-observer disagreement of 1% or less and no measurement differed by more than 6%. At the other end of the spectrum, using the NASCET method, 5% of measurements differed by 6% or more.

The study found that the NASCET method underestimated the degree of stenosis compared to the ECST and CC methods, while the ECST and CC methods had almost identical results (Staikov *et al.* 2000).

A comparison of all three methods in over 1000 patients randomised in ECST found that the ECST and CC methods differed from the NASCET method in more than 50% of measurements with twice as many stenoses being classified greater than 70% when the ECST and CC methods were used (Rothwell *et al.* 1994a). Since the relations between measurements were approximately linear, they could be converted by a simple equation (equations 3 and 5).

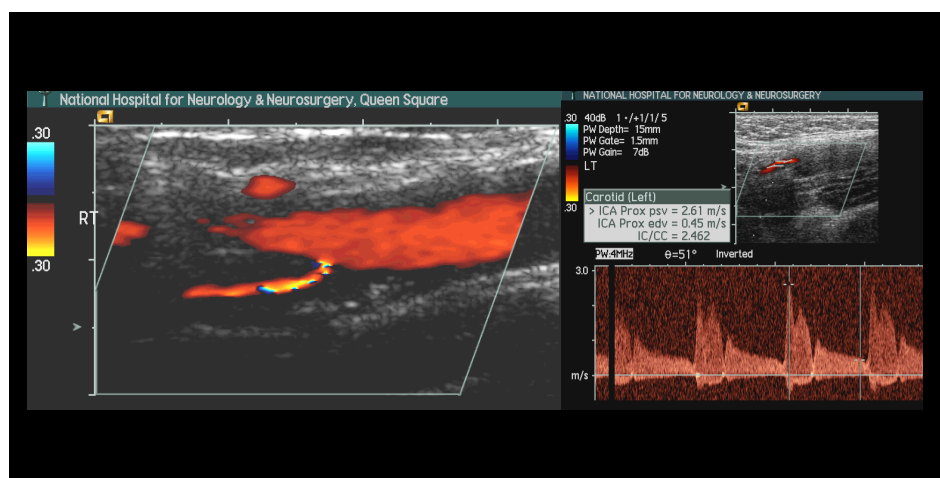
Because the Common Carotid method proved to be the most reproducible of the three it was recommended to adopt the CC method as the standard method of measuring the degree of carotid stenosis on angiograms (Rothwell *et al.* 1994b). However, this view has not gained much traction and NASCET remains the method used more widely to measure carotid stenosis on angiogram.

## Ultrasound

Non-invasive carotid ultrasound has replaced conventional angiography as first-line imaging modality for carotid stenosis when CT angiography is not available. Carotid stenosis is best evaluated by a combination of duplex and Doppler techniques. While the stenosis can be visualised using duplex ultrasound, colour-coded Doppler ultrasound measures blood-flow velocities (Figure 8.12).

**Figure 8.12 – Carotid Doppler ultrasound of carotid artery stenosis**

Shown are colour Doppler and flow-velocity measurements of a carotid stenosis. Images courtesy P.Sidhu.



In the hands of an experienced operator the sensitivity and specificity of carotid ultrasound reaches 90% for the presence of severe carotid stenosis. However, carotid ultrasound is very user-dependant and calcifications or tortuous arteries may make an accurate measurement of stenosis difficult. The technique is also limited by the inability to insonate the distal internal carotid artery and it may be difficult to know whether failure to obtain a good ICA signal is due to occlusion of the vessel or simply technical.

#### Flow Velocity Criteria of Measuring Carotid Stenosis

Neither the NASCET, ECST, nor common carotid method described above are useful in measuring carotid stenosis by carotid ultrasound, which has the great advantage of being a non-invasive imaging modality.

Criteria for estimating carotid stenosis by measuring peak systolic and end diastolic flow velocities has been established by the Society of Radiologists in Ultrasound Consensus Conference (Grant *et al.* 2003).

**Table 8.1 – Doppler ultrasound flow velocity criteria for estimating the degree of carotid stenosis**

*PSV, peak systolic velocity; EDV, end diastolic velocity; ICA, internal carotid artery; CCA, common carotid artery. Adopted from (Sidhu et al. 1997)*

| Stenosis (%) | PSV ICA (m/s) | EDV ICA (m/s) | PSV ICA/PSV CCA |
|--------------|---------------|---------------|-----------------|
| 0 – 29       | < 1.0         | < 0.4         | < 3.2           |
| 30 – 49      | 1.1 – 1.3     | < 0.4         | < 3.2           |
| 50 – 59      | > 1.3         | < 0.4         | < 3.2           |
| 60 – 69      | > 1.3         | 0.4 – 1.1     | 3.2 – 3.9       |
| 70 – 79      | > 2.1         | 1.2 – 1.4     | ≥ 4.0           |
| 80 – 95      | > 2.1         | > 1.4         | ≥ 4.0           |
| 96 – 99      | String Flow   | String Flow   | String Flow     |
| Occlusion    | Occluded      | Occluded      | Occluded        |

Similar criteria (shown in Table 8.1) are used in the local ultrasound laboratory (Sidhu *et al.* 1997). The technique relies primarily on the increase in peak systolic velocity with increasing stenosis. PSV is the most accurate parameter for a stenosis between 50% and 90%.

Above 90% stenosis, the PSV falls as stenosis approaches occlusion (Brant *et al.* 2006). Carotid occlusion may be difficult to distinguish from severe carotid stenosis using carotid ultrasound. Relying on the lack of pulsation of the vessel wall alone to detect carotid occlusion is insufficient (Thiele *et al.* 1992). Internal Carotid Stenosis is characterised by an increasing spectral broadening, or an increase in the frequency range of the Doppler signal. In expert hands, colour Doppler ultrasound allows for a narrow channel of blood-flow to be identified.

Carotid ultrasound has been compared to catheter angiography and it has been shown that results of carotid Doppler ultrasound correlate well with catheter angiography (Eliasziw *et al.* 1995; Chen *et al.* 1998; Dinkel *et al.* 2001). It has therefore largely replaced catheter angiography as first line imaging modality of carotid artery stenosis. However, ultrasound is very subjective and user-dependant.

### **MR Angiography With or Without Contrast Agent**

Magnetic resonance angiography allows for imaging of the extracranial and main cerebral arteries and can identify the location of a thrombus and visualised recanalisation (Blatter *et al.* 1993; Nederkoorn *et al.* 2003). Time-of-flight MRA (TOF-MRA) is used to visualise the Circle of Willis, contrast-enhanced MRA (CEMRA) is preferred for the imaging of the cervical arteries because it is able to visualise arteries distal to the occluded segment (Alfke *et al.* 2011).

TOF-MRA is a gradient-echo sequence that relies on the differences in exposure to radiofrequency pulses between in-plane saturated stationary tissue protons and blood flowing into the plane (Hoffmann *et al.* 2012). Slow flow is difficult to differentiate from occlusion using TOF-MRA and susceptibility artefacts from vessel wall calcification may

limit its use but overall has a similar sensitivity to CEMRA in detecting extracranial internal carotid artery stenosis greater than 70% (Debrey *et al.* 2008). Contrast-enhanced MRA relies on intravenous contrast agents to reduce the T1 relaxation time of tissue and generates contrast between intravascular lumen and surrounding tissue relatively independent from flow dynamics (U-King-Im *et al.* 2009).

Subacute intraluminal clots in dissection appear T1 hyperintense and may be mistaken for flow on TOF-MRA. When dissection is suspected, a fat-saturated T1-weighted sequence may help to distinguish the two.

The main disadvantages of MR angiography are its cost and the duration of imaging acquisition. Metal implants or claustrophobia may rule it out in a proportion of patients and MR scanners are still not available everywhere. While it is a safe technique, concerns have recently been raised about the safety of paramagnetic contrast agents in patients with renal impairment (Kuo *et al.* 2007; Heinz-Peer *et al.* 2009).

### CT Angiography

The development of fast spiral CT scanners has added CT angiography to the arsenal of imaging modalities available for measuring carotid stenosis and has replaced carotid ultrasound as first line imaging modality for carotid stenosis in hyper-acute stroke patients. It can accurately detect large intracranial and extracranial vessel stenosis and occlusion (Bash *et al.* 2005; Tan *et al.* 2007). In acute stroke patients this is of prognostic importance as terminal carotid T occlusions, proximal MCA occlusion and tandem lesions tend to respond poorly to intravenous thrombolysis and may be candidates for intra-arterial thrombolysis or mechanical clot removal (Hoffmann *et al.* 2012).

CT angiography can also demonstrate collateral blood supply to the ischaemic region, with presence of good collateral flow linked to better outcome (Miteff *et al.* 2009).

An additional benefit of CTA is its ability to identify other pathologies such as arterio-venous malformations or cerebral aneurysm.

Severe renal impairment precludes the inclusion of CTA in the work up of patients due to the use of injected iodinated contrast agents. Of great advantage is the relative speed of acquiring images covering a section from the aortic arch to the top of the head. Speed and area covered is dependent on the number of detectors used in the CT scanner and will likely increase further in the future.

#### **8.5.4 Future of Carotid Imaging**

The diagnosis of carotid stenosis in need of treatment is currently primarily based on the degree of narrowing and does not take into account lessons from coronary artery stenosis in particular. It is now widely accepted that not necessarily the degree of narrowing but the composition of the plaque causing the stenosis determines outcome in coronary artery disease (Naghavi *et al.* 2003). This has been shown to also apply to the carotid artery (Spagnoli *et al.* 2004). Histopathological studies identified components of carotid atheroma (large lipid core, thin or ruptured fibrous cap, and intra-plaque haemorrhage) that are associated with an increased risk of stroke (Spagnoli *et al.* 2004; Redgrave *et al.* 2006). High-resolution MRI has emerged as a promising technique for *in vivo* carotid atheroma imaging (U-King-Im *et al.* 2004; Davies *et al.* 2005; Trivedi *et al.* 2007; U-King-Im *et al.* 2009). Several studies have shown that MRI can successfully identify the different plaque components associated with an increased risk of stroke (Toussaint *et al.* 1996; Fayad *et al.* 2000; Clarke *et al.* 2003; Moody *et al.* 2003; Trivedi *et al.* 2004; Yuan *et al.* 2004; Ouhlous *et al.* 2005; Saam *et al.* 2005; Takaya *et al.* 2005; Sadat *et al.* 2009). In the future these additional factors may play a bigger role in selecting patients for intervention (Gillard 2007). The future role of CT and MR will be to guide therapy by excluding other pathology, characterising location and subtype of stroke and assessment of risk of haemorrhagic transformation. The challenge will be to minimise the time to reperfusion and equipping ambulances with CT scanners may be one way of achieving this (Walter *et al.* 2012).

## 8.6 Treatment of Stroke With Particular Reference to Carotid Artery Stenosis

### 8.6.1 Medical Treatment

Medical treatment of carotid stenosis is aimed at preventing recurrent stroke through modification of cardiovascular risk factors. Apart from life-style changes (diet, exercise, smoking), three major risk factors are addressed: hypertension, hypercholesterolaemia and risk of atherothrombosis. Recommendations regarding the management of risk factors have changed over the years as insight into disease development and progression increased. This process is likely to continue and the following discussion of the rationale of treating risk factors in symptomatic patients (secondary prevention) reflects current practice at the time of writing.

#### Hypertension

The European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) have defined different grades of hypertension (Table 8.2) and published guidelines when and how to treat hypertension (Graham *et al.* 2007).

**Table 8.2 – Definition and classification of blood pressure levels**

*Isolated systolic hypertension should be graded (I, II, III) according to systolic blood pressure values in the ranges indicated, provided the diastolic values are < 90 mmHg. Adopted from (Graham *et al.* 2007)*

| Category                       | Systolic (mmHg) |        | Diastolic (mmHg) |
|--------------------------------|-----------------|--------|------------------|
| Optimal                        | < 120           | and    | < 80             |
| Normal                         | 120 – 129       | and/or | 80 – 84          |
| High normal                    | 130 – 139       | and/or | 85 – 89          |
| Grade I hypertension           | 140 – 159       | and/or | 90 – 99          |
| Grade II hypertension          | 160 – 179       | and/or | 100 – 109        |
| Grade III hypertension         | ≥ 180           | and/or | ≥ 110            |
| Isolated systolic hypertension | ≥ 140           | and    | < 90             |

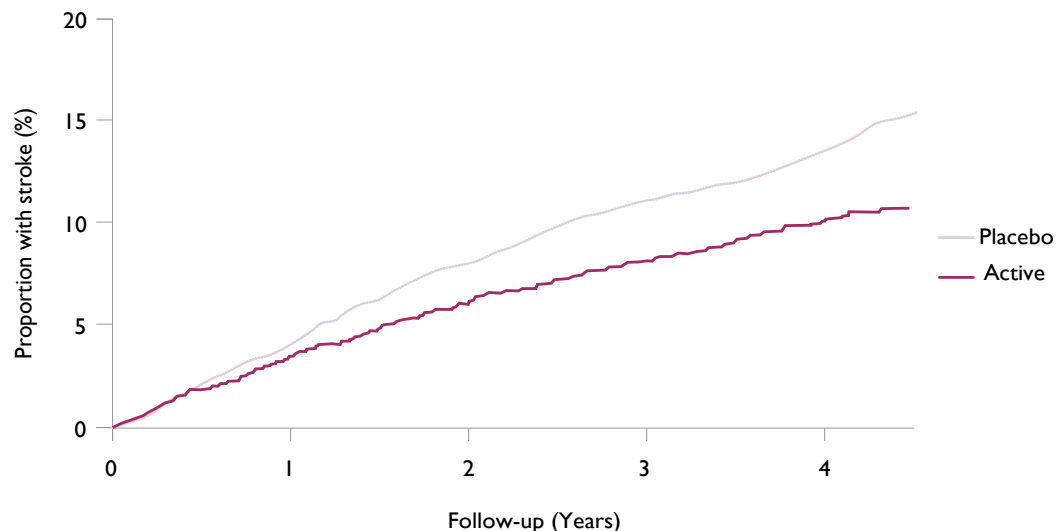


Blood pressure (BP) lowering in patients with transient ischaemia or stroke was found to significantly reduce the risk of stroke (Rashid *et al.* 2003). This was the case regardless of the patient fulfilling criteria for hypertension or not. The correlation between blood pressure and cardiovascular risk appears to be linear with systolic blood pressure being a slightly better predictor of outcome than diastolic blood pressure. A combination of angiotensin-converting enzyme (ACE) inhibitors and diuretics seemed to be more effective than ACE inhibitors alone or the combination of  $\beta$ -blockers and diuretics (Rashid *et al.* 2003).

This confirmed findings of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), which tested an ACE inhibitor (perindopril) alone ( $n = 1,281$  patients) and in combination with a diuretic (indapamide) ( $n = 1,770$  patients) in hypertensive and normotensive patients with TIA or stroke within the preceding 5 years in comparison to placebo treatment ( $n = 3,054$  patients) (MacMahon *et al.* 2001). Hypertension was unusually defined as a blood pressure greater than 160/90 mmHg.

**Figure 8.13 – PROGRESS: Cumulative incidence of stroke**

Cumulative incidence of stroke in patients assigned to active treatment versus placebo. Reprinted from (MacMahon *et al.* 2001) with permission from Elsevier.



The combination treatment was the most effective in lowering blood pressure. Active treatment reduced the 4-year risk of stroke from 14% to 10% (Figure 8.13). While double

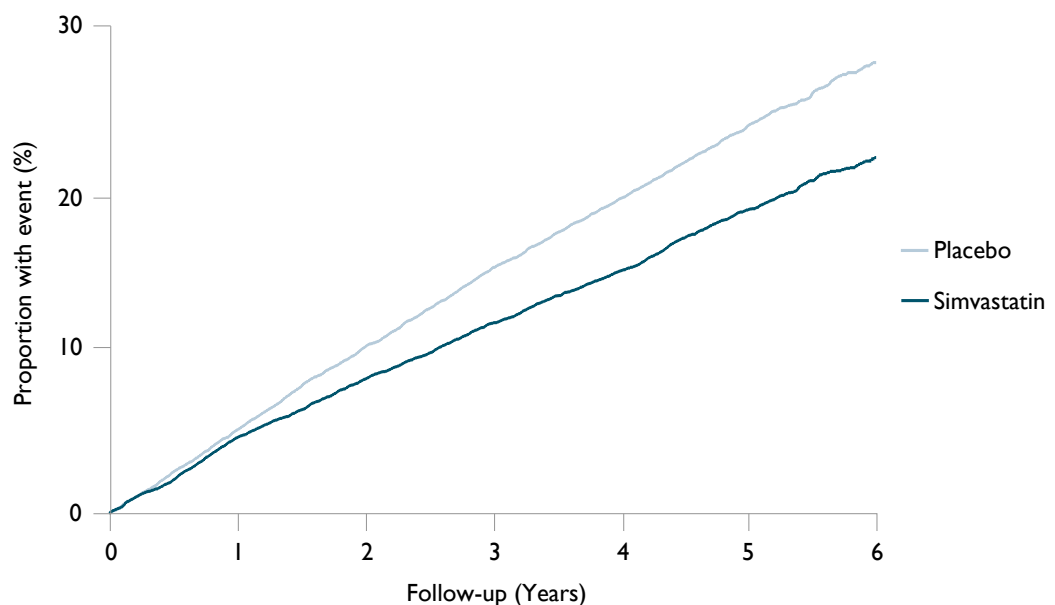
active treatment led to a significant 43% relative risk reduction, perindopril alone was not significantly better than placebo in preventing stroke. This probably reflects the difference in blood pressure lowering achieved with different regimes.

### Hypercholesterolaemia

The Heart Protection Study investigated the long-term effects of cholesterol-lowering therapy on mortality and morbidity in patients at high risk of vascular events from a wide range of circumstances by comparing 40 mg simvastatin daily (n = 10,232 patients) to placebo (n = 10,237 patients) (Collins *et al.* 2002). Simvastatin significantly reduced the 5-year risk of any vascular event from 25.2% to 19.8% (Figure 8.14), and the 5-year risk of any stroke more modestly from 5.7% to 4.3% (a 25% relative risk reduction).

**Figure 8.14 – Heart Protection Study: Cumulative incidence of any vascular event**

Shown is the cumulative incidence of any vascular event in patients randomised to 40 mg simvastatin or placebo. Reprinted from (Collins *et al.* 2002) with permission from Elsevier.



The incidence of carotid endarterectomy and angioplasty was halved in the active treatment group (from 82 [0.8%] in the placebo group to 42 [0.4%] in the active treatment group,  $p = 0.0003$ ) consistent with findings by other studies that cholesterol lowering

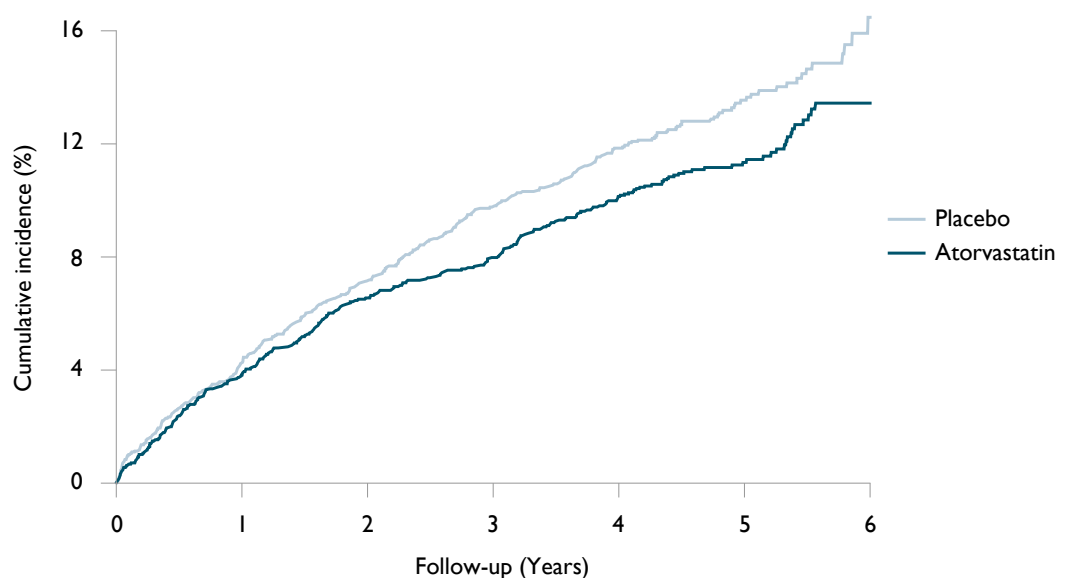
reduced the need for coronary artery revascularisation (Pedersen *et al.* 1994; Sacks *et al.* 2000).

More recently, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study allocated patients after TIA or stroke to receive either 80 mg atorvastatin (n = 2,365 patients) or placebo (n = 2,366 patients) (Amarenco *et al.* 2006). High-dose atorvastatin reduced the 5-year risk of fatal or non-fatal stroke from 13.1% to 11.2% (hazard ratio 0.87, 95% CI 0.71 to 0.99, p = 0.03, Figure 8.15), but there was also a small increase in the risk of cerebral haemorrhage associated with statin use (hazard ratio 1.66, 95% CI 1.08 to 2.55).

The SPARCL trial also showed a significant reduction in carotid revascularisation from 7.2% in the placebo group to 3.2% in the active treatment group in patients with carotid artery stenosis (HR 0.44, 95% CI 0.24 to 0.79). The risk of stroke was reduced from 16.1% in the placebo group to 11.2% in the active treatment group in the same patients (Sillesen *et al.* 2008).

**Figure 8.15 – SPARCL: Kaplan-Meier plot of fatal or non-fatal stroke**

Shown is the cumulative incidence (%) of fatal or nonfatal stroke in patients randomised to 80 mg atorvastatin or placebo. Reprinted from (Amarenco *et al.* 2006) with permission from The New England Journal of Medicine.



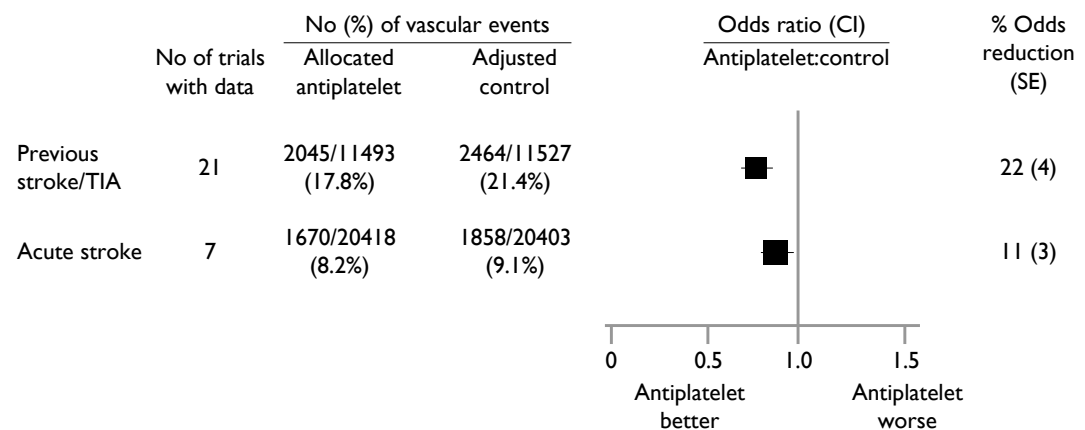
## Antiplatelets

Aspirin was originally introduced 113 years ago as pain relief and antipyretic medication. More than 70 years later, Sir John Robert Vane (1927 – 2004) discovered the therapeutic mechanism of aspirin – the inhibition of prostaglandin synthesis. For this discovery he was honoured with the Nobel Prize for Physiology or Medicine in 1982. Today aspirin has become a mainstay in preventive treatment for heart attack and stroke after clinical trials in the 1960s and thereafter had established its efficacy as an anti-clotting agent. Although the overall benefit is relatively minor, the low cost of aspirin makes it the most widely prescribed drug in secondary prevention of stroke.

Several meta-analyses have shown that antiplatelets are effective in preventing stroke in secondary prevention studies of various vascular diseases (Figure 8.16) (Collins *et al.* 1994; Baigent *et al.* 2002). A meta-analysis of placebo-controlled trials of aspirin after TIA or stroke revealed a relative risk reduction of vascular death, stroke and MI of 13% (Algra *et al.* 1999). A small trial in patients with asymptomatic carotid stenosis failed to show any long-term protective effect of aspirin (Cote *et al.* 1995).

**Figure 8.16 – Proportional effects of antiplatelet therapy on stroke and TIA**

Stratified Odds of an event in the treatment groups compared to that in control groups (black square) and its 99% CI (horizontal line). Adjusted controls have been calculated after converting any unevenly randomised trials to even ones by counting control groups more than once. Statistical calculations are based on actual numbers from individual trials. Reprinted from (Baigent *et al.* 2002) with permission from BMJ Publishing Group Ltd.



Medium dose aspirin (75 to 325 mg daily) is the most widely tested regimen and initially no other regimen appeared significantly more effective in preventing stroke (Collins *et al.*

1994). Barnett and colleagues investigated different doses of aspirin in patients undergoing carotid endarterectomy and found that in fact a lower dose of aspirin (81 mg to 325 mg daily) was associated with a lower risk of stroke, myocardial infarction and death within 30 days and three months after endarterectomy than a higher dose of aspirin (650 mg and 1300 mg).

Since then, several other studies have compared different antiplatelet agents. The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial compared clopidogrel (n = 9,599 patients) and aspirin (n = 9,586 patients) in patients with MI, stroke or peripheral vascular disease (PVD) (Gent *et al.* 1996). Clopidogrel was associated with a very modest relative risk reduction of 8.7% for the combined primary endpoint of myocardial infarction, stroke or vascular death compared to aspirin. However the difference was not statistically significant in patients with stroke. There were less severe side effects associated with clopidogrel.

The Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) Trial compared the combination of clopidogrel plus aspirin to aspirin alone in patients with recently symptomatic carotid stenosis. The dual-therapy was more effective in preventing the primary endpoint of asymptomatic microembolic signals on transcranial Doppler (TCD), a possible marker of future stroke and TIA in these patients (Markus *et al.* 2005). Microembolic signals were detected in 43.8% of patients taking dual-antiplatelet therapy compared to 72.7% with aspirin alone, a relative risk reduction of 39.8% (95% CI 31.6 to 78.2, p = 0.0013).

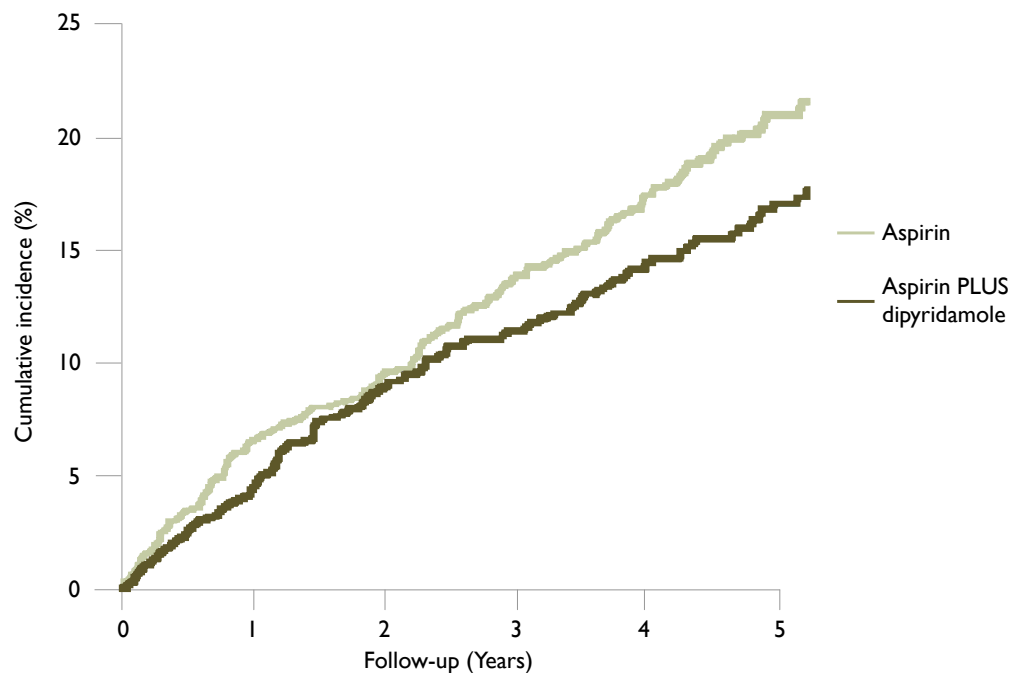
The Management of Atherothrombosis with Clopidogrel in High-risk Patients (MATCH) study sought to investigate if the addition of aspirin to clopidogrel improved the beneficial effect of clopidogrel alone (Diener *et al.* 2004). The study assigned 3,797 patients to the combination therapy and 3,802 patients to clopidogrel alone. The investigators found no statistically significant difference for the primary endpoint of myocardial infarction, stroke, vascular death or hospitalization. But the risk of life-

threatening bleeding was significantly higher in the combined treatment group. The combination of aspirin and clopidogrel is therefore reserved for special indications such as failure of other antiplatelet therapy, i.e. in patients suffering a cerebrovascular event while on alternative antiplatelet regimen or to cover the periprocedural period of carotid endarterectomy or stenting.

The European/ Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) was undertaken to resolve uncertainty raised by a Cochrane Review (De Schryver *et al.* 2003a; De Schryver *et al.* 2003b) surrounding the secondary preventive value of combined dipyridamole and aspirin (Halkes *et al.* 2006). Patients were assigned to a combination of 30 mg to 325 mg aspirin daily plus 200 mg dipyridamole twice daily (n = 1,363 patients) or the same dose of aspirin alone (n = 1,376 patients) and followed up for a mean of 3.5 years. The combination therapy reduced the risk of death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complication from 15.7% to 12.7%, a 1% reduction *per annum* (Figure 8.17).

**Figure 8.17 – ESPRIT: Kaplan-Meier plot for the primary outcome measure**

Shown is the cumulative incidence (%) of death from all vascular causes, non-fatal stroke, non-fatal MI and non-fatal major bleeding complication. Reprinted from (Halkes *et al.* 2006) with permission from Elsevier.

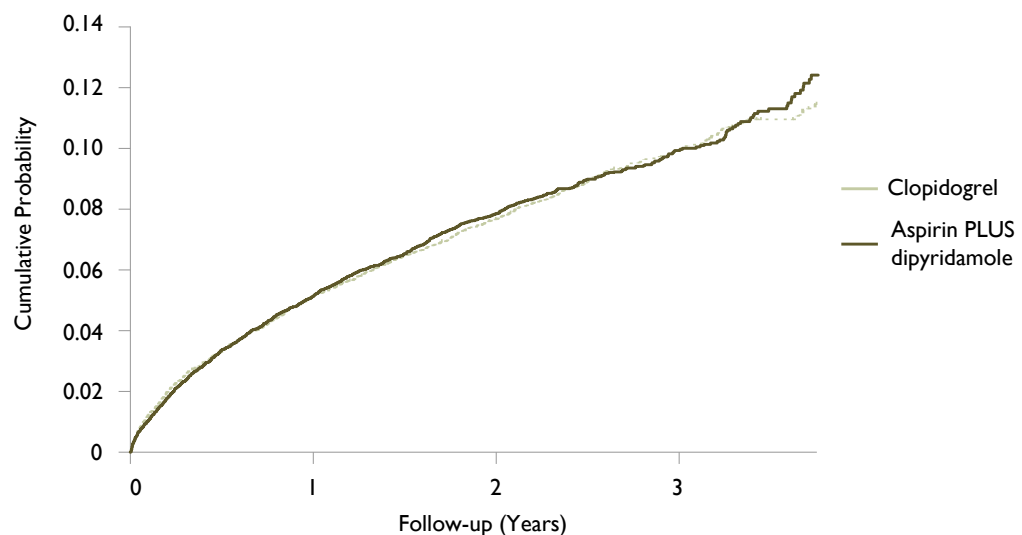


This finding was consistent with an update of the Cochrane Review (De Schryver *et al.* 2007; De Schryver *et al.* 2008) and the combination of aspirin plus dipyridamole was subsequently recommended by the National Institute for Health and Clinical Excellence in secondary prevention of stroke (National Institute for Health and Clinical Excellence 2008).

The Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) Study compared 25 mg aspirin plus 200 mg extended-release dipyridamole twice daily (n = 10,181 patients) to 75 mg clopidogrel (n = 10,151 patients) in patients with a recent ischaemic stroke (Sacco *et al.* 2008). The primary outcome of recurrent stroke was recorded in 916 patients (9.0%) receiving aspirin plus dipyridamole and 898 patients (8.8%) receiving clopidogrel over a mean follow-up period of 2.5 years (HR 1.01, 95% CI 0.92 to 1.11). Figure 8.18 shows the cumulative probability of the primary outcome measure in PROFESS.

**Figure 8.18 – PROFESS: Risk of recurrent stroke for clopidogrel and aspirin plus dipyridamole**

Shown is the cumulative probability of recurrent stroke. Reprinted from (Sacco *et al.* 2008) with permission from The New England Journal of Medicine.



In the UK, aspirin plus dipyridamole initially remained the antiplatelet regimen of choice. This was mainly due to cost-effectiveness consideration with clopidogrel being

almost five times more expensive than the combination of aspirin plus extended-release dipyridamole (£ 1.26 *versus* £ 0.27 per daily dose).

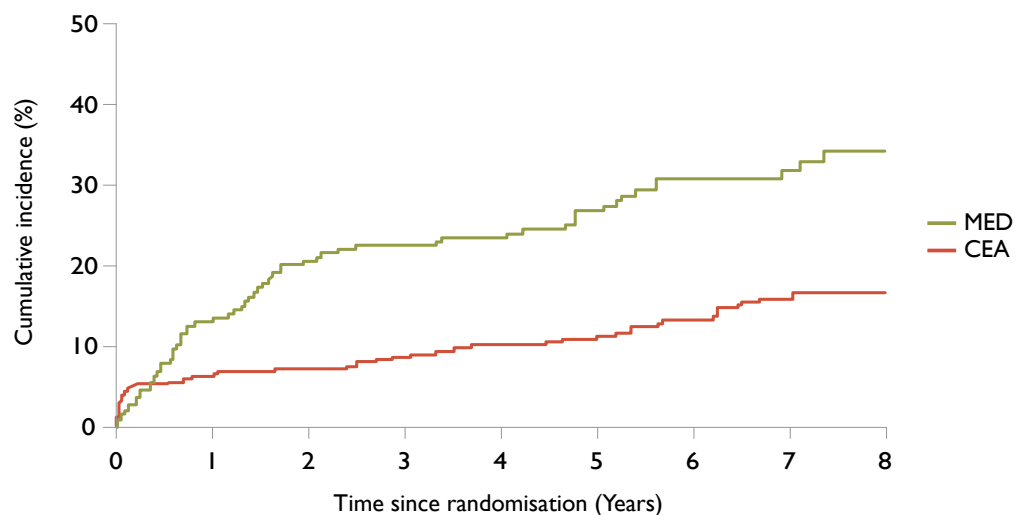
However, clopidogrel is now out of licence which has led to it being available at a much lower cost (£ 0.11 per daily dose) and NICE has recently recommended that clopidogrel is now the antiplatelet agent of choice for stroke prevention, in preference to aspirin, with aspirin plus dipyridamole as the second choice in patients unable to tolerate clopidogrel (National Institute for Health and Clinical Excellence 2010).

### 8.6.2 Surgical Treatment of Internal Carotid Artery Stenosis

While the secondary prevention measures outlined above should also apply to patients with carotid artery stenosis, the high risk of recently symptomatic carotid stenosis suggests that they do not work quickly enough. Data from the large surgery trials seems to show that it may take two years for best medical treatment to develop its protective potential (Figure 8.19).

**Figure 8.19 – European Carotid Surgery Trial: Kaplan-Meier incidence of major stroke**

*This graph shows the cumulative incidence of major stroke in surgery and control patients with 80 to 99% stenosis. Note that after 2 years the lines for each treatment start to run roughly parallel suggesting that medical therapy takes 2 years to develop its full protection. Reprinted from (Farrell et al. 1998) with permission from Elsevier.*



Eliminating the stenosis as a possible source for infarction, be it haemodynamic or thrombo-embolic, in order to further reduce the risk of stroke in patients with carotid



stenosis appears to be logical. The publication of Debakey's case series of carotid surgery in predominantly symptomatic patients (Debakey *et al.* 1965) created immense interest in the technique and after reports that endarterectomy may help prevent stroke in patients with asymptomatic carotid stenosis (Thompson *et al.* 1978), carotid endarterectomy soon became one of the most frequently carried out surgical procedures in both asymptomatic and symptomatic patients. Spirits were dampened after concerns were raised about the appropriateness of treating symptomatic patients (Fields *et al.* 1970; Shaw *et al.* 1984). This prompted the setting up of large clinical trials comparing carotid endarterectomy and medical therapy. The Veterans Affairs 309 (VA309) study (Mayberg *et al.* 1991) was prematurely halted after the North American Symptomatic Carotid Endarterectomy Study (NASCET) and the European Carotid Surgery Trial (ECST) had published interim results in favour of carotid endarterectomy in patients with severe stenosis (North American Symptomatic Carotid Endarterectomy Trial Collaborators 1991; Peto *et al.* 1991). Their main results shall now be discussed followed by a discussion of a combined analysis of the VA309 study, NASCET and ECST (Rothwell *et al.* 2003).

### Symptomatic Carotid Artery Stenosis

ECST recruited patients who had experienced symptoms attributable to carotid stenosis (i.e. TIA, amaurosis fugax, retinal infarction, or non-disabling stroke) in the six months leading up to randomisation. The degree of stenosis had to be confirmed by catheter angiography and there had to be "substantial uncertainty" as to whether carotid endarterectomy should be recommended (Peto *et al.* 1991; Farrell *et al.* 1998). Patients were then randomised to either undergo immediate surgery (n = 1,811 patients) or deferred surgery (n = 1,213 patients). Medical treatment was to be similar in both groups. "Appropriate" medical therapy included aspirin, treatment of definite hypertension and advice to stop smoking (Peto *et al.* 1991). Unfortunately, the trial provided little information on compliance with this treatment regimen. The trial did not specify a minimum degree of stenosis to qualify for participation. The degree of stenosis

was distributed equally between the greater than 70%, 50 to 69% and less than 50% stenosis groups, as measured by the ECST criteria. The mean follow-up was 6.1 years.

The trial showed that carotid endarterectomy was associated with a substantial 7% risk of death and stroke lasting more than 7 days (i.e. major stroke) in the 30 days following surgery. Nevertheless, surgery reduced the risk of ipsilateral major stroke over the course of three years from 20.6% to 6.8% ( $p < 0.0001$ ) and that of any major stroke or death from 26.5% to 14.9% ( $p = 0.001$ ) in patients with stenosis greater than 80% (ECST criteria). No effect of surgery was shown for stenosis below 70 to 80% (ECST criteria). Interestingly, the trial showed that age and sex had a significant effect on the frequency of major stroke or death. The conclusions that can be drawn from ECST are that the balance of risk and benefit is in favour of surgery with severe stenosis of about 80% (ECST criteria) and that surgery is riskier in women than in men (Farrell *et al.* 1998).

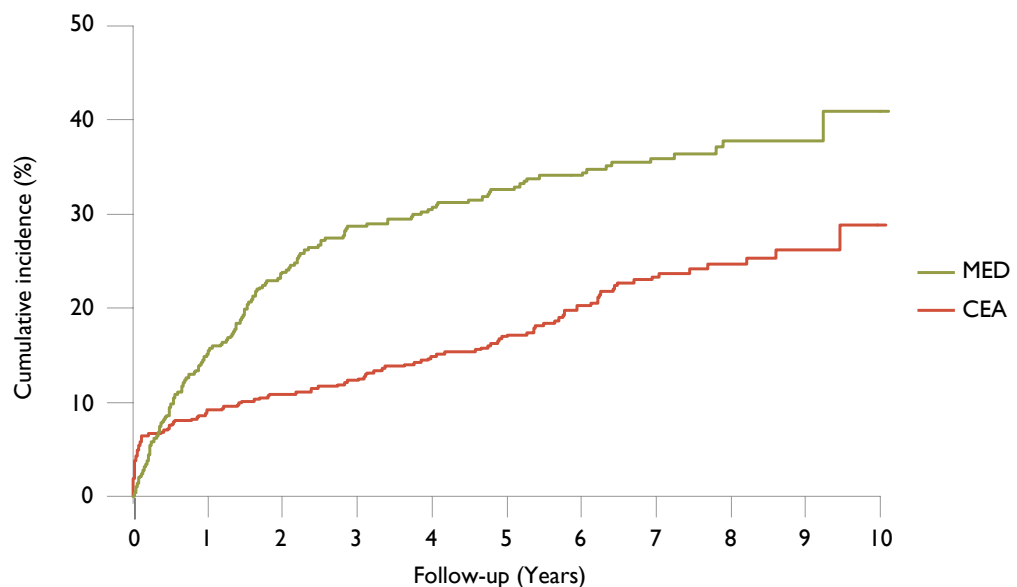
NASCET was carried out at the same time and had similar inclusion criteria. Initially, patients were eligible if focal cerebral ischaemia in the distribution of the carotid artery (i.e. one or more TIA or non-disabling stroke) had occurred no more than 120 days prior to randomisation (Barnett *et al.* 1991), this threshold was raised at some stage to 180 days (Barnett *et al.* 1998). Confirmation of carotid stenosis was by angiography and the minimum stenosis required by the protocol was 30% (NASCET criteria). Patients were randomised between surgery ( $n = 1,436$  patients) and no surgery ( $n = 1,449$  patients). Medical treatment in both arms consisted of aspirin and treatment of hypertension and (in contrast to ECST) hypercholesterolaemia (Barnett *et al.* 1991). The risk of stroke or death in the 30 days following surgery was 5.8% in patients with greater than 70% stenosis ( $n = 328$ , NASCET criteria) and 6.7% in the remaining patients in the surgery group. In the former patient group, surgery reduced the risk of ipsilateral stroke at two years by 17%. The benefit was smaller with less severe stenosis: The absolute risk reduction at five years achieved by surgery was 6.5% ( $p = 0.045$ ) in patients with 50 to 69% stenosis (NASCET criteria) and a non-significant 3.8% ( $p = 0.16$ ) in patients with 30

to 49% stenosis as measured by NASCET criteria (Barnett *et al.* 1998). These results were consistent with the ECST data.

In order to make the trials more easily comparable the ECST angiograms were re-measured using the NASCET criteria, outcome events re-defined and a combined analysis of ECST, NASCET and the VA309 study carried out (Rothwell *et al.* 2003). The risk of stroke or death in the 30 days following surgery was 7.1% in the combined population and 6.4% in patients with stenosis exceeding 70%. The pooled analysis confirmed findings from the individual trials that the benefit gained from carotid endarterectomy depends on the degree of stenosis. The risk of any stroke or perioperative death was reduced following surgery by 15.6% in patients with 70 to 99% stenosis (Figure 8.20). In patients with 50 to 69% stenosis the risk reduction was a more modest 7.8%. While surgery in carotid near-occlusion and less than 50% stenosis was in fact associated with no benefit at all (Figure 8.21).

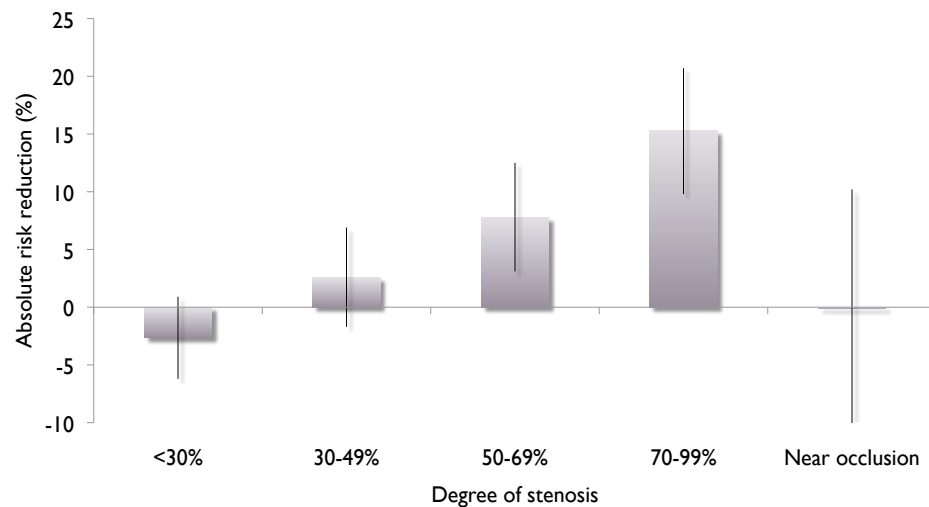
**Figure 8.20 – NASCET, ECST, and VA study: Risk of any stroke or operative death**

Cumulative incidence of stroke or operative death in patients with 70 to 99% stenosis excluding near occlusions in the pooled data. Reprinted from (Rothwell *et al.* 2003) with permission from Elsevier.



**Figure 8.21 – NASCET and ECST: Effect of surgery on the absolute risk of any stroke or operative death**

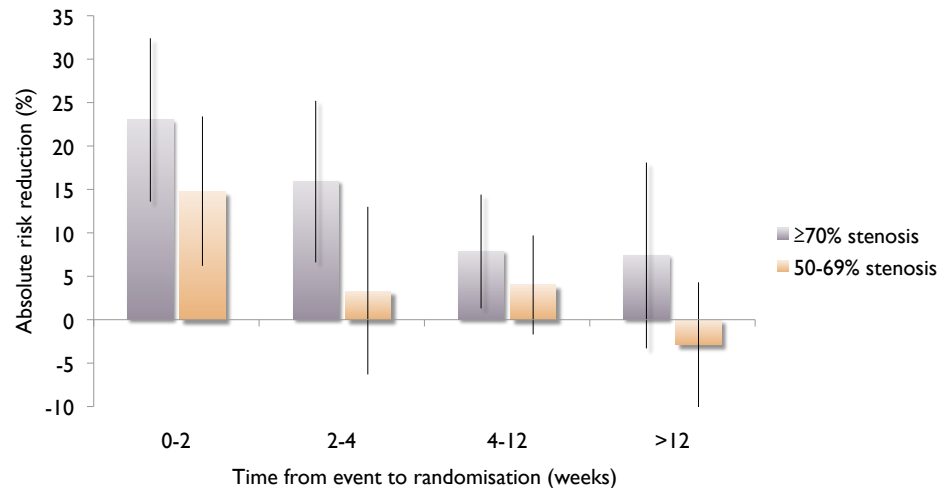
Absolute risk reduction after 5 years of follow-up by degree of stenosis and intention to treat. Vertical lines represent the 95% CI. Adopted from (Rothwell *et al.* 2003).



Various subgroups of patients from NASCET and ECST were also combined to compare patients with carotid stenosis  $\geq 50\%$  as well as timing of carotid endarterectomy (Rothwell *et al.* 2004b). It found that men tended to have a greater benefit from surgery than women. In men the absolute reduction in the cumulative 5-year risk of ipsilateral carotid ischaemic stroke and any stroke or death within 30 days was 11.0% (95% CI 7.6 to 14.4%) compared to a non-significant risk reduction of only 2.8% (95% CI -2.2 to 7.8%) in women. Elderly patients older than 75 years (ARR 19.2%, 95% CI 10.2 to 28.2%) also benefited more from carotid endarterectomy than patients under the age of 65 years (ARR 5.6%, 95% CI 1.6 to 9.6%). Figure 8.22 illustrates that the benefit of surgery decreased with time since last symptoms (Rothwell *et al.* 2004b).

**Figure 8.22 – NASCET and ECST: Absolute reduction in the risk of ipsilateral carotid ischaemic stroke and any stroke or death within 30 days after trial surgery**

Shown is the absolute risk reduction with surgery in the 5-year cumulative risk of ipsilateral carotid ischaemic stroke and any stroke or death within 30 days after trial surgery in patients with 50 – 69% stenosis and  $\geq 70\%$  stenosis depending on time since event. Vertical lines indicate 95% confidence intervals. Reprinted from (Rothwell *et al.* 2004b) with permission from Elsevier.



These findings have restored the confidence in carotid endarterectomy and firmly established carotid endarterectomy as treatment of choice in patients with symptomatic severe carotid stenosis. One peri-operative death or stroke for every six patients with carotid stenosis  $\geq 70\%$  undergoing carotid endarterectomy is prevented by carotid endarterectomy. Twice as many patients with moderate carotid stenosis (50 to 69%) need to undergo carotid endarterectomy to prevent one peri-operative death or stroke.

### Asymptomatic Carotid Artery Stenosis

Similar trials to the symptomatic surgery trials described above were carried out in patients in whom the carotid stenosis had not yet caused stroke or TIA (Diener *et al.* 1991; Mayo Asymptomatic Carotid Endarterectomy Study Group 1992; Hobson *et al.* 1993; Toole *et al.* 1995; Halliday *et al.* 2004).

Two trials will not be discussed in great detail because of shortcomings in study design. The Carotid Artery Stenosis with Asymptomatic Narrowing: Operation versus Aspirin study (CASANOVA) compared 410 patients (Diener *et al.* 1991). However, it did not

strictly compare surgery to medical treatment because patients with bilateral stenosis did have surgery on the more affected side and there were large numbers of cross-overs. The Mayo Asymptomatic Carotid Endarterectomy (MACE) Study did not include aspirin as regular treatment in the surgery arm (Mayo Asymptomatic Carotid Endarterectomy Study Group 1992).

The Veterans Affairs (VA) study compared carotid endarterectomy in male patients with arteriographically proven carotid stenosis greater than 50% (Hobson *et al.* 1993). A total of 444 patients (mean age 64.5 years) were randomised to either undergo carotid endarterectomy plus aspirin or medical therapy alone, including aspirin. The authors did not further elaborate on the exact nature of medical treatment. Surgery led to a significant reduction in the absolute risk of stroke, TIA and monocular blindness of 12.6% (relative risk 0.38, 95% confidence interval 0.22 to 0.67), but the combined incidence of stroke or death did not differ between the two groups during the mean follow-up of two years.

The studies making the biggest impact on treatment of asymptomatic carotid stenosis and shaping today's approach to the condition were the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST) (Toole *et al.* 1995; Halliday *et al.* 2004).

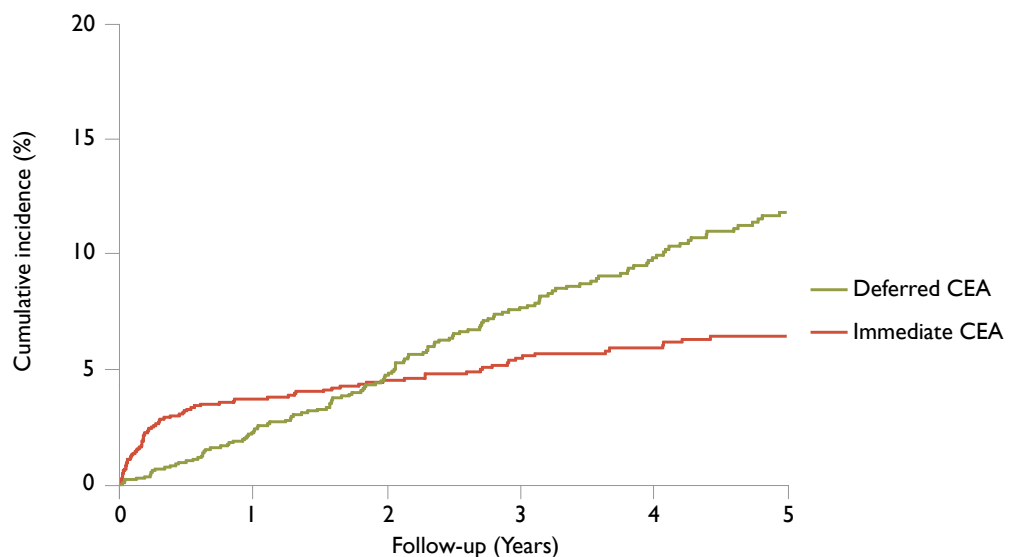
ACAS recruited 1,662 patients who were diagnosed with asymptomatic carotid stenosis greater than 60% (Toole *et al.* 1995). The degree of stenosis was confirmed by formal angiography using the NASCET criteria to measure stenosis. Medical treatment consisted of 325 mg aspirin plus risk factor modification; surgery was carried out by the preferred method of the surgeon as soon as possible after randomisation. Patients were followed up for a median 2.7 years. ACAS showed a significant reduction in the estimated 5-year risk of ipsilateral stroke or death (including any perioperative stroke or death) in the surgery group from 11% to 5.1%. This equates to a very small reduction in absolute annual risk over five years of 1.2%. However, the reduction in stroke only

became apparent in the fifth year of follow-up and other endpoints did not show any significant difference between the two groups.

ACST was an even bigger study of 3,120 patients (Halliday *et al.* 2004). Patients were included if the carotid stenosis was narrowed to less than 60% of its luminal diameter as measured by ultrasound. They were randomised between immediate and delayed surgery. Therefore some patients in the latter group had an endarterectomy if they became symptomatic or developed another definite reason for surgery during follow-up (Halliday *et al.* 2004). Unfortunately, the spectrum of “definite” indications for surgery where not provided. No specific medical regimen was prescribed by the study protocol and surgeons chose their preferred method of carrying out the carotid endarterectomy as soon as possible after randomisation. Surgery led to a significantly reduced 5-year risk of any type of stroke or perioperative death from 11.8% to 6.4% (Figure 8.23), equating to a small annual reduction in absolute risk of about 2%.

**Figure 8.23 – ACST: Any type of stroke or perioperative death**

Shown is the cumulative incidence of any stroke or perioperative death. Reprinted from (Halliday *et al.* 2004) with permission from Elsevier.



While these results may be perceived as headline-grabbing figures promoting carotid endarterectomy in healthy and asymptomatic patients it is important to keep some

important findings in mind. ACAS showed that only men benefited from surgery and in ACST the benefit for women was much smaller than in men. Additionally, the benefit was greater in younger patients and a large number of patients had unnecessary surgery. In ACST, 50 patients needed to be treated in order to prevent one stroke or peri-operative death per year. In ACAS, the number needed to treat in order to prevent one ipsilateral stroke death was 83.

#### **Note of Caution**

Impressive and compelling as the results of the surgery trials may appear to be, a note of caution has to be sounded. In all these trials surgery was compared to a medical treatment that by today's standards could very well be regarded as substandard. Current guidelines for secondary prevention of stroke differ greatly to those in existence at the time of ECST, NASCET, ACAS, and ACST. Aspirin had already found its way into the secondary prevention arsenal of medications at the time of the surgery trials. The benefit of lipid-lowering drugs, which are now a mainstay of medical therapy in stroke prevention, only became fully apparent after the publication of the Heart Protection Study (Collins *et al.* 2002). It could be argued that the benefit of carotid endarterectomy over medical therapy would be much lower today, especially in asymptomatic patients. Since statins take up to one year to develop their protective potential it is less likely that medical treatment has a big influence on the outcome of symptomatic stenosis given the high early risk of recurrence associated with this disease.

#### **8.6.3 Endovascular Treatment of Internal Carotid Artery Stenosis**

Non-randomised case series, non-randomised trials and registries were the only source of data providing some evidence on the risks and benefits of endovascular treatment prior to the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS). However, they were based on small numbers that prohibit drawing firm conclusions from them and they will not be discussed in detail but briefly summarised in the following chapter.



## 8.7 Hypotheses Tested in This Thesis

The studies described within this thesis had been designed to investigate several aspects regarding the safety and efficacy of endovascular treatment of carotid artery stenosis in patients with recent symptoms in comparison to carotid endarterectomy in those patients suitable for surgery and medical treatment in patients not suitable for surgery. The work attempted to identify factors that may be associated with particular risks of one procedure. Particular emphasis was placed on identifying radiological parameters that may help to identify patient groups more suitable for one treatment or the other. The studies were large randomised, multi-centre clinical trials.

The main null hypothesis of this thesis is that endovascular treatment is of similar safety and efficacy than carotid endarterectomy in patients with symptomatic carotid stenosis suitable for either treatment. This null hypothesis is tested by

- Comparing the short-term risk of endovascular treatment with or without stenting to carotid endarterectomy within 30 days after the procedure
- Comparing the long-term durability of endovascular treatment with or without stenting in terms of preventing stroke with carotid endarterectomy.

Not all patients are suitable for surgery for various reasons. The null hypothesis that endovascular treatment of carotid stenosis was superior to medical therapy alone in these patients is tested by

- Comparing the short-term risk and long-term effectiveness of endovascular treatment and medical therapy alone.

Pre-existing small vessel disease may be a risk factor for procedural stroke following surgery or endovascular treatment. The null hypothesis that small vessel disease poses a risk for stroke after treatment that is similar in both treatment groups is tested by

- Comparing the risk of stroke associated with and without small vessel after endovascular treatment and carotid endarterectomy in patients with symptomatic carotid stenosis disease.

Published evidence of randomised clinical trials of endovascular treatment is thoroughly reviewed and combined in a meta-analysis in order to place the findings of the trials presented in this thesis into their wider context.

## 9 The Carotid And Vertebral Artery Transluminal Angioplasty Study

### 9.1 Rationale for CAVATAS

After Klaus Mathias had carried out the first carotid angioplasty to treat atherosclerotic stenosis successfully in 1981 (Mathias 1981), anxieties about the risks associated with carotid angioplasty persisted and it was not recommended to carry out the procedure in the carotid artery (Perry *et al.* 1983). Cerebral embolism caused by dislodged atheromatous material or thrombus from the vessel wall or as a result of dissection of the carotid artery at the time of balloon inflation with subsequent thromboembolism was considered to be the major risk of percutaneous transluminal angioplasty (PTA). Cerebral ischaemia caused by hypo perfusion during the time of balloon inflation was thought to be another potential mechanism of causing damage to the brain. Also of concern was the risk of restenosis, a well-recognised risk of PTA at other sites.

However, by 1992, the time the first patient was randomised in CAVATAS several case series of endovascular treatment of carotid artery stenosis had been published (Bockenheimer *et al.* 1983; Wiggli *et al.* 1983; Tsai *et al.* 1986; Freitag *et al.* 1987; Brown *et al.* 1990; Theron *et al.* 1990; Kachel *et al.* 1991; Munari *et al.* 1992). These case series reported not a single case of minor non-disabling or major stroke in over 100 patients and it was thought that endovascular treatment might be an alternative to carotid endarterectomy, which had been firmly established as treatment of choice by the large surgical trials.

Encouraged by these preliminary findings, albeit in a very small number of patients and thus acutely aware of the need for randomised data from a much larger patient population to assess the safety of carotid balloon angioplasty, the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) was set up and registered with the International Standard Randomised Controlled Trial Number Register (ISRCTN Register,

No. 01425573). Its initial aim was to provide information about the safety of endovascular treatment compared to carotid endarterectomy within 30 days after the procedure. In addition and even more importantly, it aimed at collecting long-term follow-up data about the efficacy and durability of endovascular treatment.

CAVATAS consisted of three distinct trials. The largest trial compared endovascular treatment and carotid endarterectomy in patients suitable for surgery (Brown *et al.* 2001). This study is the one most often referred to as CAVATAS. A second trial compared endovascular treatment and stand-alone medical therapy in patients with vertebral artery stenosis (Coward *et al.* 2007). A third trial compared endovascular treatment to stand-alone medical therapy in patients with carotid stenosis not suitable for surgery and became known as CAVATAS-MED.

CAVATAS and CAVATAS-MED will be described and discussed in detail in this chapter. Parts of the work have been presented at the European Stroke Conferences 2007 (Ederle *et al.* 2007b) and 2008 (Ederle *et al.* 2008a) and aspects of both bodies of work have been published in peer-reviewed journals (Brown *et al.* 2001; McCabe *et al.* 2005; Bonati *et al.* 2009; Ederle *et al.* 2009a; Ederle *et al.* 2009b).

## 9.2 Endovascular Treatment versus Surgery in Patients Suitable for Surgery

### 9.2.1 Methods and Patients

#### Trial Centres

Centres wishing to participate in CAVATAS were required to have a team in place consisting of a neurologist or physician with an interest in stroke medicine, a vascular surgeon or neurosurgeon experienced in carotid endarterectomy, and a radiologist trained in neuroradiology and the technique of angioplasty. The experience of each participating investigator was assessed by a credentials subcommittee to ensure that each centre had sufficient expertise to join the trial. Radiologists from experienced centres provided training to centres with little experience in cerebrovascular angioplasty.

CAVATAS was a collaboration of 22 centres in Europe, Australia and Canada. The collaborating centres are listed in the Appendix.

### **Patients**

Patients were eligible for inclusion in CAVATAS if they had stenosis of the common carotid artery, carotid bifurcation or internal carotid artery that was thought by the investigators to require treatment. Patients had to be equally suitable for both carotid endarterectomy and endovascular treatment and they were only included if the local investigators were unsure of the best treatment option.

Patients were excluded from the trial if they were unwilling or unable to provide informed consent, if angiography demonstrated a thrombus or if the patient had suffered a major stroke with no useful recovery of function in the territory of the treatable artery. The presence of intracranial stenosis beyond the skull base and stenosis unsuitable for endovascular treatment also excluded patients from participating in CAVATAS. No age limits were specified in the inclusion criteria.

### **Investigations prior to Randomisation**

Investigators were allowed to use their local protocol to investigate patients and establish the degree of carotid stenosis. Most centres used ultrasound in the first instance confirmed by conventional angiography before randomisation. Centres that were able to provide data from audits showing a high degree of accuracy compared to conventional angiography were allowed to randomise patients on the basis of non-invasive techniques (MRA, CTA, or ultrasound). Non-invasive imaging techniques were usually carried out in combination.

Copies of angiographic or non-invasive imaging were submitted to the central office where concealed assessment and measurement of stenosis was carried out. Stenosis of both carotid arteries was measured using the Common Carotid Method on the best available angiogram. In the patients in whom only ultrasound measurements were

available ( $n = 7$ ) flow-velocity criteria (Sidhu *et al.* 1997) were used to estimate the degree of stenosis.

### **Randomisation**

Randomisation was carried out by telephone or fax to the randomisation centre at the Clinical Trial Service Unit in Oxford, UK after informed consent was obtained. A computerised minimisation algorithm was used for random treatment allocation. It took into account centre and timing of symptoms (symptoms within six months prior to randomisation and more distant symptoms) to achieve balanced numbers of patients in both groups.

### **Treatment**

#### **Surgery**

The allocated treatment was to be carried out as soon as possible after randomisation. Surgeons were allowed to use their preferred technique. No requirements with regards to anaesthesia, the use of shunts or patches, or use of heparin during the procedure were specified by the trial protocol.

#### **Endovascular Treatment**

Angioplasty was carried out using percutaneous transluminal interventional techniques as soon as possible after randomisation. Before 1994, this was done by balloon angioplasty. Stents suitable for the carotid artery became available in 1994 and their use was allowed if the interventionist carrying out the procedure believed this to be necessary. They could be used either as primary technique or secondary after balloon inflation. Cerebral protection devices were allowed but not mandatory. No requirements with regards to guide wires, catheters, premedication, local anaesthesia, or atropine use were set by the protocol. The protocol did specify that all patients randomised to endovascular treatment should receive 150 mg of aspirin or an alternative antiplatelet agent for at least 24 hours prior to the procedure. Patients were systemically

anticoagulated with 5,000 units of heparin during and for 24 hours after the procedure. Antiplatelet therapy was to be continued throughout follow-up.

#### Medical Treatment

The CAVATAS protocol did not specify a specific medical treatment regimen for risk factor control. It was left to the discretion of the individual centres to manage patients' cardiovascular risk factors according to local guidelines and protocols. Hypertension, diabetes mellitus and hypercholesterolaemia were identified in the protocol as the risk factors to be addressed as part of the medical treatment regimen in addition to an antiplatelet agent or anticoagulant as appropriate.

#### Follow-up

Patients randomised to surgery and endovascular treatment were followed up at one month after treatment. Further follow-up was carried out six months and yearly after randomisation for at least five years in both treatment groups. An independent clinician not directly involved in surgery or endovascular treatment carefully conducted follow-up. Ultrasound was used to assess the patency of the treated carotid artery but this was not compulsory because ultrasound was not available at all participating centres at the start of the trial. Annual ultrasound follow-up was encouraged where it was available.

Peak systolic velocities (PSV) in the common carotid artery (CCA) and internal carotid artery (ICA), and end diastolic velocity (EDV) in the ICA were recorded and reported to the central office. Pre-defined standardised flow velocity criteria were used to estimate the degree of stenosis (Table 8.1, page 56).

Stenosis was classified as not significant (0 to 49%), moderate (50 to 69%), severe (70 to 99%), or occluded (100%). In the small number of centres, where individual velocity measurements were not reported the local ultrasonographer's estimate of stenosis was used.

All outcome events were reported to the central trial office where researchers unaware of allocated treatment independently adjudicated outcome events by reviewing all available clinical information.

### **Definition of Outcome Events**

Stroke was classified as fatal if death occurred as a direct result of stroke at any time after the event. Stroke leading to patients requiring help from another person in carrying out activities of daily living (corresponding to a modified Rankin score of three or more) was classified as disabling. The remaining stroke events were classified as non-disabling and divided into those that lasted for fewer than 7 days and those that lasted for more than 7 days. This classification matched the criteria used in ECST, which only reported strokes lasting more than 7 days (Farrell *et al.* 1998).

Strokes that lasted for fewer than 7 days and transient ischaemic attacks were not included in the primary analysis to avoid a bias due to under-reporting of minor symptoms in patients operated under general anaesthesia and returned to intensive care units or surgical wards where they were not routinely seen by a neurologist. Long-term outcome measures did include TIA and minor strokes because it was thought that any under-reporting of minor events would be balanced in both groups since an independent clinician followed up all patients.

Death occurring from any cardiovascular-related illness other than stroke was classified as other vascular death. Death caused by non-vascular-related illness was classified as non-vascular. If no information about the cause of death was available it was classified as undetermined. UK patients were registered with the General Register Office (GRO) to identify deaths in all patients randomised within the UK.

Outcome events were classified as perioperative if they occurred at the time of treatment or within 30 days after treatment. The date of crossover to medical treatment in patients who did not undergo their allocated treatment was defined as proxy-treatment date for the purpose of statistical analysis.



## Outcome Measures

### Primary Outcome Measure

The primary outcome measure of CAVATAS was defined by the protocol as

- Long-term period free of disabling stroke or death from the time of randomisation.

The trial was designed to provide information to inform the clinician about the value of the different treatment options to the patient and the health service. Death was included in the primary outcome measure because it has direct bearing on the cost-effectiveness of treatment, which was regarded as an important issue to be addressed. It was anticipated that the trial would include mainly elderly patients and mortality was thought to be particularly important. This was to be investigated by comparing the differences in life years free of disability and hence the rate of disabling stroke or death was chosen as primary outcome measure.

### Secondary Outcome Measures

The trial protocol did not pre-specify any additional outcome measures. Many aspects are worth taking into account when trying to assess the safety and efficacy of endovascular treatment compared to surgery and a number of secondary endpoints were defined prior to the analysis of data. They were:

- Stroke lasting more than 7 days or death
- Any stroke or perioperative death
- Stroke lasting more than 7 days or perioperative death.

Further secondary analyses excluded perioperative events and death of non-stroke related causes to assess the long-term efficacy of endovascular treatment compared to surgery:

- Stroke or TIA occurring more than 30 days after treatment
- Stroke occurring more than 30 days after treatment
- Ipsilateral stroke or TIA occurring more than 30 days after treatment
- Ipsilateral stroke occurring more than 30 days after treatment
- Contralateral stroke more than 30 days after treatment.
- Any cause of death

Any cause of death was analysed separately because it was anticipated that most outcome events over such a long time of follow-up would be due to death rather than stroke.

Restenosis was a well-recognised problem of endovascular treatment. It was unclear if restenosis was a benign occurrence or associated with an increase risk in stroke. A separate analysis was performed to shed light on this issue.

### **Subgroup Analyses**

Several subgroups were defined prior to the analysis. Patients who received a stent were compared to those who underwent balloon angioplasty alone to investigate how the use of stents influenced the rate of stroke lasting more than 7 days or perioperative death.

Additionally, several baseline characteristics were chosen that might influence outcome based on findings from other studies and knowledge about risk factors for stroke. Those were age (dichotomized at the median), sex, severity of ipsilateral and contralateral stenosis, severity of qualifying event, hypertension, diabetes mellitus, smoking, history of ischaemic heart disease, and previous myocardial infarction.

The combined endpoint of stroke lasting more than 7 days or perioperative death was chosen to carry out the subgroup analyses.

## Statistical Methods

CAVATAS was an exploratory trial and no formal sample size calculation had been carried out. The duration of recruitment was determined by availability of funding. All data were analysed using standard statistical software (SPSS for Macintosh, SPSS Inc., Chicago, Illinois, USA).

The log rank test was used to compare the survival free experience in the two treatment arms. The treatment effect was estimated using a Cox proportional hazard model to calculate hazard ratios and 95% confidence intervals (CI). The carotid endarterectomy group was used as the reference group throughout. The proportional hazards assumption was tested with a graphical log-minus-log method. All outcome events up to the last available follow-up or death of the patient were included in the calculation of hazard ratios.

The number of patients followed up for more than eight years dropped to less than 50 and Kaplan-Meier curves were therefore only plotted up to eight years after randomisation. Patients experiencing more than one event were only counted once in each category with the first corresponding event, whenever it occurred.

Primary and secondary outcome measures were analysed by intention to treat, i.e. patients were analysed in their randomly allocated treatment group regardless of whether they received the allocated treatment or not. Additionally, all outcome measures were analysed by allocated treatment received, i.e. only patients who received their allocated treatment were included in the analysis (per-protocol analysis).

The exploratory subgroup analyses were done by intention to treat. The comparison of stenting, balloon angioplasty alone and carotid endarterectomy was based on the allocated treatment received (per protocol). Cox regression was used to test for treatment effect interaction within the subgroups.

Restenosis data were analysed by intention to treat but a secondary per-protocol analysis was also carried out. For the comparison of restenosis after angioplasty alone *versus* stenting the per-protocol data set was used. Time to censoring was compared with a log rank test to reveal differences in duration of ultrasound follow-up between the groups. Since the exact date on which restenosis had occurred was unknown, a generalised non-linear model was used to compare the groups. Patients free of restenosis were censored at the time of the last ultrasound investigation and censoring was assumed to be non-informative. The proportionality of hazards was assessed via interactions with follow-up time periods. Hazard ratios and corresponding 95% confidence intervals were calculated for the entire duration of follow-up. Life-table analyses estimated the cumulative incidences of restenosis at the scheduled ultrasound investigation after treatment, with a pre-defined interest in the incidences after one and five years of follow-up. In cases of restenosis and missing data from the preceding follow-up appointment, restenosis was arbitrarily assumed to have occurred mid way between the date the diagnosis of restenosis was made and the last available ultrasound investigation showing no stenosis.

To test if  $\geq 70\%$  restenosis during follow-up is associated with pre-defined covariates multivariable generalised non-linear models adjusted for treatment were used. The calculation of hazard ratio was subsequently adjusted for age, sex, and independent predictors of restenosis as identified by the above-mentioned analysis. Cox regression analyses were used to compare time until occurrence of ipsilateral cerebrovascular events between patients with and without  $\geq 70\%$  carotid stenosis adjusted for allocated treatment, age and sex.

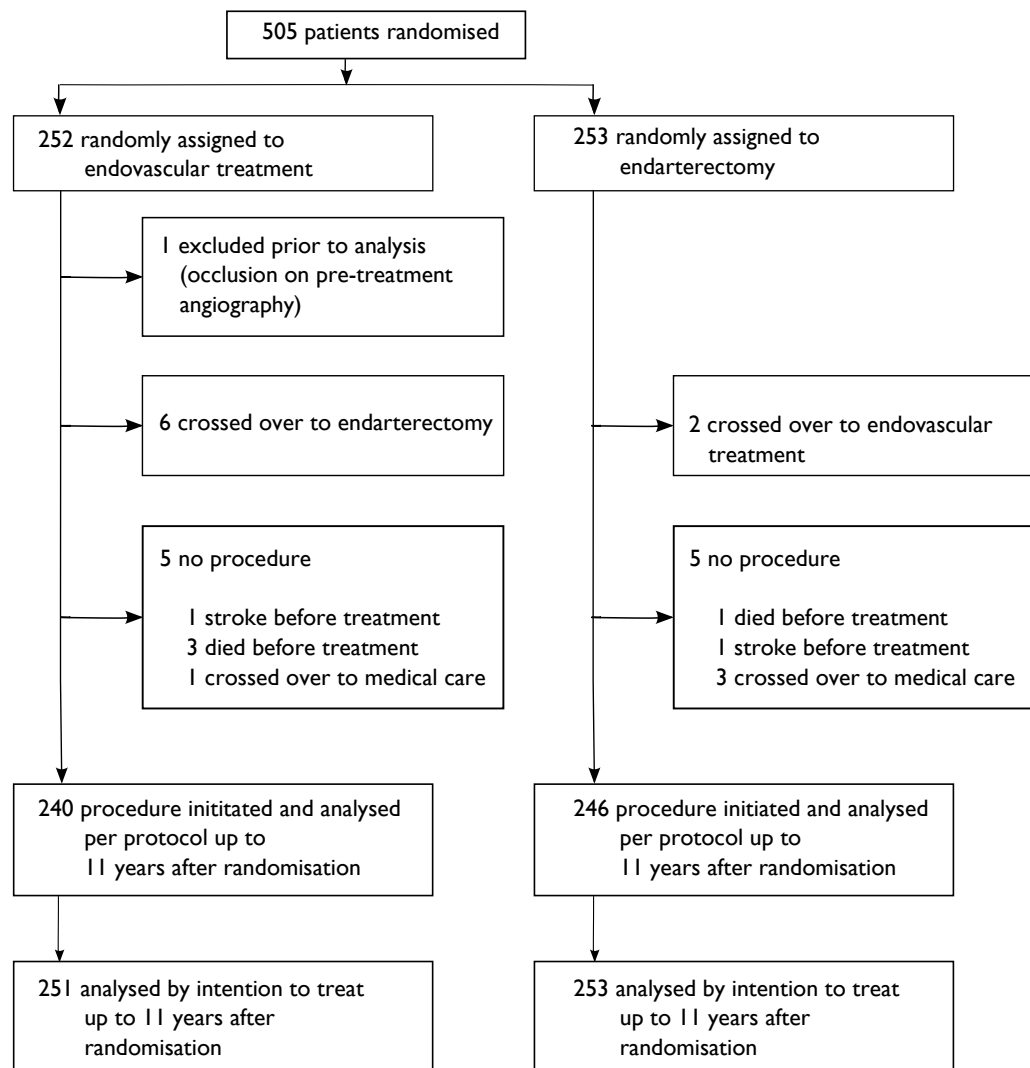
### 9.2.2 Results

#### Baseline Characteristics

Between 1 March 1992 and 31 July 1997 a total of 505 patients were randomly assigned to undergo endovascular treatment (n = 252) or carotid endarterectomy (n = 253). One patient was found to have an occluded carotid artery after randomisation but before

angioplasty was attempted. The decision was taken to exclude this patient from further analysis. This left 251 patients allocated to endovascular treatment and 253 patients allocated to carotid endarterectomy for the intention-to-treat analysis (Figure 9.1).

Figure 9.1 – CAVATAS: Trial profile



Almost 90% of patients included in the study had experienced cerebrovascular symptoms attributable to the carotid artery in the six months preceding randomisation, the majority of which were transient symptoms (Table 9.1).

**Table 9.1 – CAVATAS: Cerebrovascular events within 6 months before randomisation per allocated treatment.**

*Data are number of events (% of known data). EVT, endovascular treatment; CEA, carotid endarterectomy*

|                                   | <b>EVT<br/>(n = 251)</b> | <b>CEA<br/>(n = 253)</b> |
|-----------------------------------|--------------------------|--------------------------|
| <b>Transient ischaemic attack</b> | 94 (37%)                 | 98 (39%)                 |
| <b>Amaurosis fugax</b>            | 60 (24%)                 | 63 (25%)                 |
| <b>Hemisphere stroke</b>          |                          |                          |
| Minor                             | 19 (8%)                  | 20 (8%)                  |
| Major, non-disabling              | 32 (13%)                 | 28 (11%)                 |
| Major, disabling                  | 11 (4%)                  | 18 (7%)                  |
| <b>Retinal infarct</b>            | 5 (2%)                   | 3 (1%)                   |

More than 50% of patients were considered hypertensive and roughly 75% had a history of smoking. Cholesterol was elevated in just over one third of all patients (Table 9.2).

Roughly 85% of the patients had a baseline carotid stenosis greater than 70% measured using the Common Carotid Method. Contralateral carotid stenosis greater than 70% was only found in just under one third of all patients. In general, baseline characteristics were well balanced (Figure 9.2).

**Table 9.2 – CAVATAS: Patient characteristics at baseline per allocated treatment**

Data are number of patients (%) of known data), unless otherwise indicated. EVT, endovascular treatment; CEA, carotid endarterectomy; SD, standard deviation; IQR, interquartile range.

|  | EVT<br>(n = 251) | CEA<br>(n = 253) |
|--|------------------|------------------|
| <b>Age (median [IQR], years)</b>                                 | 68 [62 – 73]     | 68 [62 – 73]     |
| <b>Sex</b>   |                  |                  |
| Women  | 77 (31%)         | 75 (30%)         |
| Men  | 174 (69%)        | 178 (70%)        |
| <b>Vascular risk factors</b>                                     |                  |                  |
| Hypertension   | 132 (53%)        | 144 (58%)        |
| Systolic blood pressure (mean [SD], mmHg)                        | 151.8 [21.8]     | 152.6 [20.1]     |
| Diastolic blood pressure (mean [SD], mmHg)                       | 83.5 [11.8]      | 83.9 [10.7]      |
| Diabetes mellitus  | 35 (14%)         | 32 (13%)         |
| Cholesterol > 6.5 mmol/L   | 67 (34%)         | 62 (32%)         |
| Smokers, past or present   | 191 (77%)        | 192 (78%)        |
| <b>Prior history of cardio-/cerebrovascular disease</b>          |                  |                  |
| Myocardial infarction  | 43 (19%)         | 40 (17%)         |
| Ischaemic heart disease  | 95 (39%)         | 92 (37%)         |
| Atrial fibrillation  | 12 (5%)          | 12 (5%)          |
| Peripheral vascular disease                                      | 60 (24%)         | 51 (20%)         |
| Cerebrovascular symptoms > 6 months before randomization         | 21 (8%)          | 15 (6%)          |
| <b>Treatments used at randomisation</b>                          |                  |                  |
| Antiplatelet   | 216 (86%)        | 230 (91%)        |
| Warfarin   | 23 (10%)         | 28 (11%)         |
| <b>Time from randomisation to treatment (median [IQR], days)</b> | 20 [8 – 32]      | 27 [14 – 41]     |

**Table 9.3 – CAVATAS: Follow-up characteristics per allocated treatment**

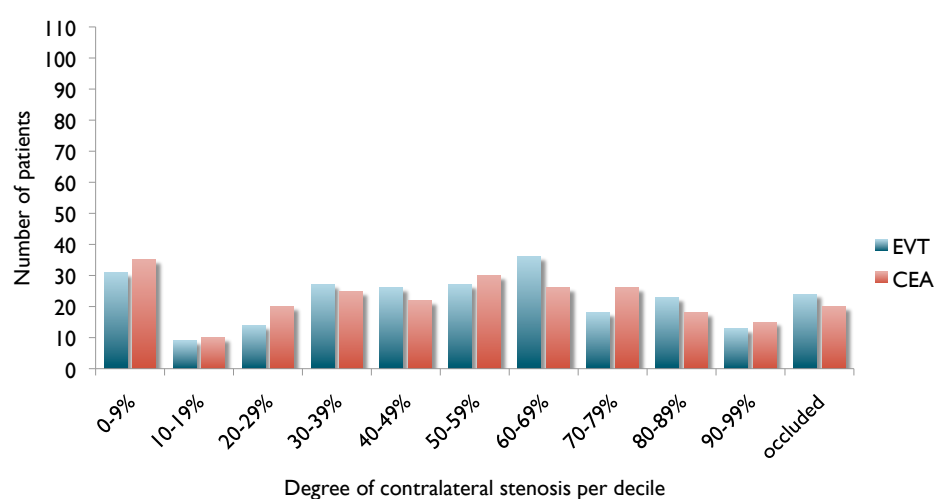
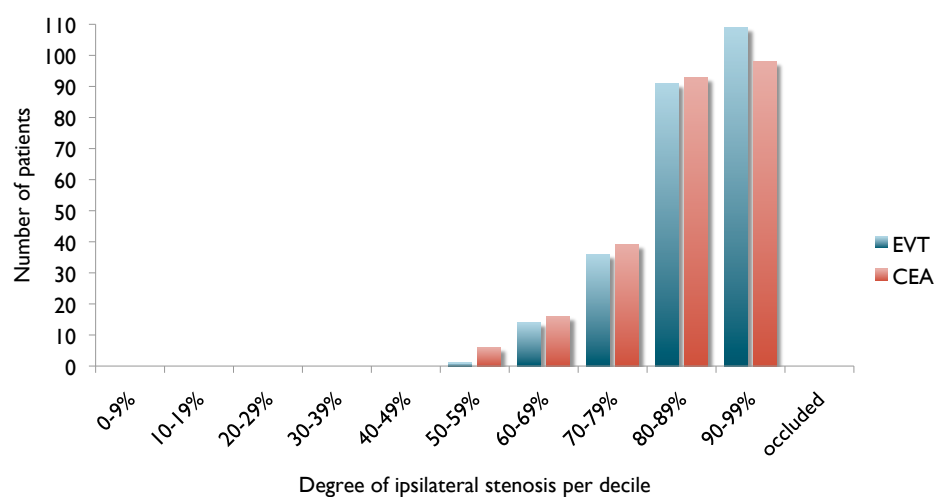
Data are number of patients (% of known data) unless otherwise indicated. EVT, endovascular treatment; CEA, carotid endarterectomy; IQR, interquartile range; SD, standard deviation. †The first line for each characteristic is taken from the 1-year follow-up, and the second line from the 6-year follow-up data.

|  | EVT<br>(n = 251)             | CEA<br>(n = 253)             |
|--|------------------------------|------------------------------|
| Follow-up median [IQR], years)   | 5 [2 – 6]                    | 5 [2 – 6]                    |
| Total person years of follow-up  | 1098                         | 1083                         |
| Use of treatments, blood pressure and smoking status during follow-up† |                              |                              |
| Antiplatelet   | 202 (92%)<br>43 (86%)        | 209 (90%)<br>47 (90%)        |
| Warfarin   | 12 (6%)<br>4 (8%)            | 12 (5%)<br>2 (4%)            |
| Systolic blood pressure (mean [SD], mmHg)                              | 151.0 [21.0]<br>153.9 [23.2] | 151.0 [23.4]<br>147.6 [26.5] |
| Diastolic blood pressure (mean [SD], mmHg)                             | 83.0 [10.1]<br>78.3 [12.3]   | 82.7 [10.2]<br>77.6 [14.0]   |
| Smokers, past or present   | 48 (23%)<br>5 (11%)          | 50 (22%)<br>12 (27%)         |



**Figure 9.2 – CAVATAS: Baseline degree of stenosis per allocated treatment**

Degree of stenosis (% per decile) in the randomised ipsilateral internal carotid artery (upper graph) and the contralateral internal carotid artery (lower graph). EVT, endovascular treatment; CEA, carotid endarterectomy.

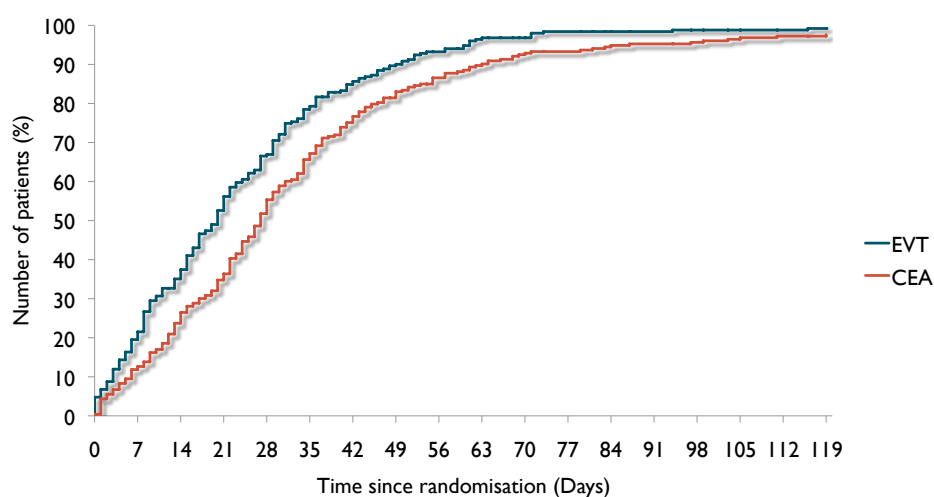


## Delay to Treatment

Patients allocated to endovascular treatment had a significantly shorter wait before treatment was administered than the patients allocated to surgery: The median delay between randomisation and endovascular treatment was 20 days (IQR 8 to 32 days) and 7 days shorter than in the surgery group (IQR 14 to 41 days,  $p < 0.001$ , Figure 9.3).

**Figure 9.3 – CAVATAS: Delay of treatment per allocated treatment**

Shown is the time between date of randomisation and date of treatment in days. EVT, endovascular treatment; CEA, carotid endarterectomy.



Three patients in the endovascular treatment group died while awaiting treatment and one patient suffered a stroke. Despite a longer delay, only one patient died and one other patient suffered a stroke in the surgery group before surgery was carried out.

Four patients received neither surgical nor endovascular treatment to the randomised artery: This was because two patients assigned to surgery were deemed unsuitable for carotid endarterectomy after randomisation and one patient in each treatment arm refused to have treatment. These patients crossed over to medical treatment.

The per-protocol analysis therefore included the 240 patients who received the allocated endovascular treatment and 246 patients who received the allocated carotid endarterectomy (Figure 9.1).

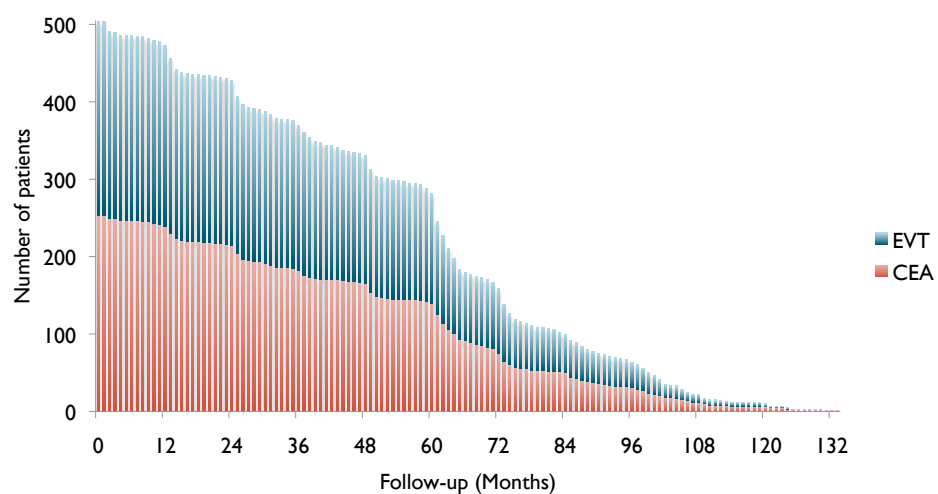
### Follow-up

Follow-up of patients was terminated in 2007 providing up to 11 years of follow-up in some patients. The median length of follow-up was identical in both treatment groups (5 years, IQR 2 to 6 years, Table 9.3).

Patients in the endovascular and endarterectomy group were followed up for a total of 1098 and 1083 person-years, respectively. Information for eight years of follow-up was available in 12.5% of the patients (Figure 9.4).

**Figure 9.4 – CAVATAS: Number of patients available for follow-up per allocated treatment**

*Absolute number of patients available for follow-up per month, regardless of an outcome event. The red (CEA) and blue (EVT) bars add up to the total number of patients. EVT, endovascular treatment; CEA, carotid endarterectomy.*



## Intention-to-treat Analyses

### Primary Outcome

#### *Disabling Stroke or Death*

Disabling stroke or death had been defined as the primary outcome measure and occurred in 117 patients in the endovascular treatment group and 121 patients in the endarterectomy group over the course of the trial.

The majority of outcome events in the primary outcome cluster were non-stroke deaths (84 in the endovascular group and 94 in the surgery group, Table 9.4). Fatal stroke was more common in the endovascular group (15 *versus* six, respectively).

The cumulative incidence of disabling stroke or death was virtually identical up to five years after randomisation and was recorded in 26.5% (SE 2.9%) of patients in the endovascular group and 27.5% (SE 3.0%) of patients in the endarterectomy group. Beyond five years the cumulative incidence of disabling stroke or death started to diverge and by eight years after randomisation it reached 45.2% (SE 4.0%) in the endovascular group and 50.4% (SE 4.1%) in the surgery group (Figure 9.5). However, the cumulative incidence subsequently converged again and the hazard ratio based on all available follow-up data showed no significant difference between endovascular treatment and surgery (HR 1.02, 95% CI 0.79 to 1.32, Figure 9.6).

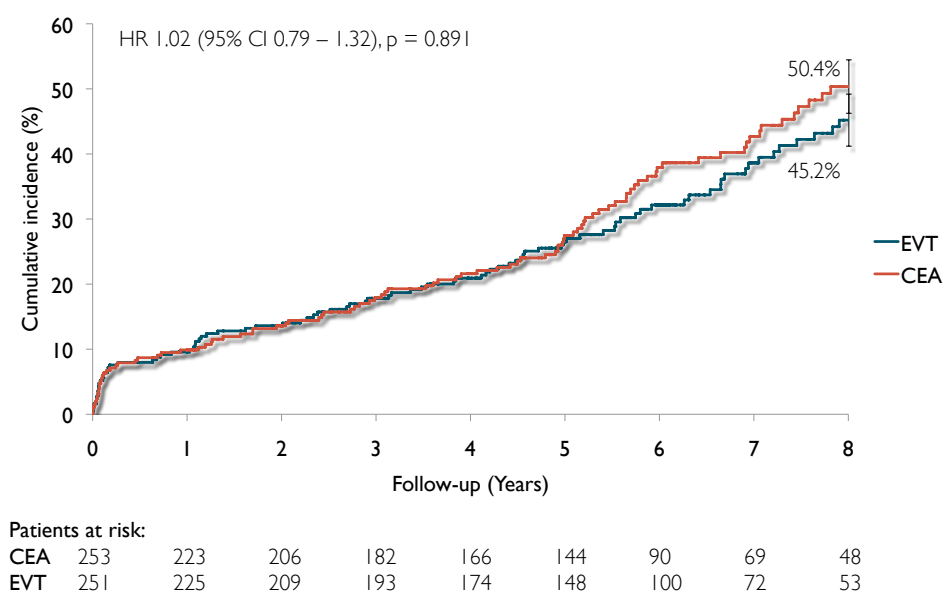
**Table 9.4 – CAVATAS: Major long-term outcome events**

Data are number of patients. Numbers in brackets indicate contribution of individual outcomes to the composite endpoint. All non-perioperative strokes lasted for more than 7 days. EVT, endovascular treatment; CEA, carotid endarterectomy. \*6 patients had a subsequent non-perioperative stroke (1 fatal, 2 disabling, 3 non-disabling). †5 patients had a subsequent non-perioperative stroke (1 fatal, 3 disabling, 1 non-disabling). ‡4 patients had a subsequent non-perioperative ipsilateral stroke (1 disabling, 3 non-disabling). §2 patients had a subsequent non-perioperative ipsilateral stroke (1 disabling, 1 non-disabling).

| Intention to treat   |                            | Per protocol                |                            |
|--|----------------------------|-----------------------------|----------------------------|
| EVT<br>(n = 251)   | CEA<br>(n = 253)           | EVT<br>(n = 240)            | CEA<br>(n = 246)           |
| <b>Disabling stroke or death</b> (disabling stroke, fatal stroke, non-stroke death)  |                            |                             |                            |
| 117<br>(18, 15, 84)  | 121<br>(21, 6, 94)         | 110<br>(18, 11, 81)         | 114<br>(19, 6, 89)         |
| <b>Stroke lasting more than 7 days or death</b> (fatal stroke, disabling stroke, non-disabling stroke, perioperative non-stroke death, non-perioperative non-stroke death)             |                            |                             |                            |
| 134<br>(14, 17, 28, 0, 75)   | 131<br>(6, 19, 22, 3, 81)  | 127<br>(11, 16, 28, 0, 72)  | 124<br>(6, 17, 22, 3, 76)  |
| <b>Any stroke or perioperative death</b> (fatal stroke, disabling stroke, non-disabling stroke > 7 days, non-disabling stroke < 7 days, vascular non-stroke death, non vascular death) |                            |                             |                            |
| 67<br>(14, 17, 28, 8, 0, 0)  | 51<br>(6, 19, 22, 1, 2, 1) | 63<br>(11, 16, 28, 8, 0, 0) | 49<br>(6, 17, 22, 1, 2, 1) |
| <b>Non-perioperative stroke or TIA</b> (fatal stroke, disabling stroke, non-disabling stroke, TIA)   |                            |                             |                            |
| 67<br>(6, 7, 18, 36*)  | 51<br>(4, 5, 9, 33†)       | 65<br>(6, 7, 17, 35*)       | 51<br>(4, 5, 9, 33†)       |
| <b>Non-perioperative ipsilateral stroke or TIA</b> (fatal stroke, disabling stroke, non-disabling stroke, TIA)   |                            |                             |                            |
| 34<br>(1, 3, 8, 22‡)   | 27<br>(1, 2, 8, 16§)       | 33<br>(1, 3, 8, 21‡)        | 27<br>(1, 3, 8, 16§)       |
| <b>Non-perioperative non-ipsilateral stroke</b> (fatal, disabling, non-disabling)  |                            |                             |                            |
| 24<br>(8, 5, 11)   | 13<br>(4, 6, 3)            | 24<br>(8, 5, 11)            | 13<br>(4, 6, 3)            |
| <b>Death</b> (stroke, vascular non-stroke, non vascular, undetermined)   |                            |                             |                            |
| 112<br>(16, 43, 44, 9)   | 113<br>(6, 53, 46, 8)      | 105<br>(14, 39, 43, 9)      | 107<br>(6, 49, 44, 8)      |

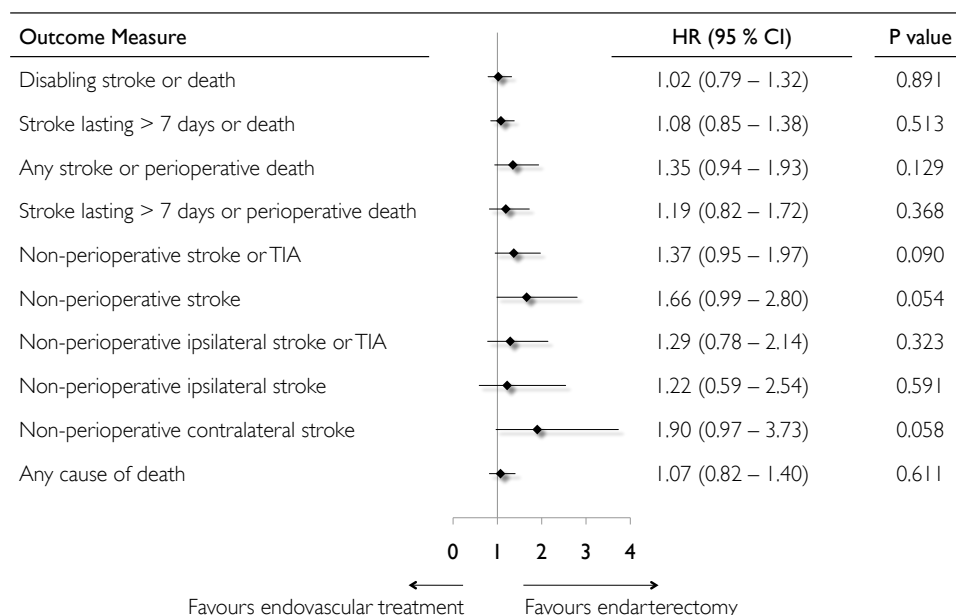
**Figure 9.5 – CAVATAS: 8-year cumulative incidence of disabling stroke or death (ITT)**

Shown is the Kaplan-Meier curve for the primary outcome measure of disabling stroke or death up to 8 years after randomisation in the intention-to-treat analysis. The vertical bars represent the standard errors of the estimated 8-year cumulative incidence. EVT, endovascular treatment; CEA, carotid endarterectomy.



**Figure 9.6 – CAVATAS: Hazard ratios for various outcome measures in (ITT)**

Hazard ratios (HR) are calculated based on the intention-to-treat data. CI, confidence interval.



## Secondary Outcome Measures

### *Safety*

Following convention, albeit a rather arbitrary one, the 30-day period following treatment has been chosen to compare the safety of endovascular treatment and carotid endarterectomy. The rate of disabling stroke or death within 30 days after first treatment was similar in both groups (6% in both treatment arms,  $p = 0.8$ , Table 9.5).

While all seven deaths within 30 days after endovascular treatment were fatal strokes, only one in four deaths following surgery were attributed to stroke. The other causes of death following surgery were ruptured aortic aneurysm, pulmonary embolism and respiratory arrest secondary to neck haematoma. In each treatment group, one patient died of non-stroke-related vascular causes without having undergone treatment. Stroke that lasted for more than seven days occurred within 30 days after endovascular treatment in 25 patients (including fatal stroke). They were 22 ischaemic strokes and three fatal haemorrhagic strokes. In 24 patients the stroke was ipsilateral to the treated artery. Following surgery, 20 ischaemic strokes lasting more than seven days and two non-disabling haemorrhagic strokes were recorded, all of which were ipsilateral to the treated vessel.

Patients appeared to be at highest risk of treatment-related stroke on the day of treatment with 16 strokes lasting longer than seven days occurring on the treatment day in either group. All but one stroke took place within two weeks after treatment (Figure 9.7). Non-disabling stroke that lasted for fewer than seven days was more common in the endovascular treatment group compared to surgery (eight *vs.* one event, respectively).

Cranial nerve injury was completely avoided by endovascular treatment. As a result of surgery it occurred in 22 patients ( $p < 0.0001$ ). All but one cranial nerve injuries resolved completely within 30 days. One cranial nerve injury did not resolve until after six months.

Haematoma requiring intervention or leading to an extended hospital stay was caused by endovascular treatment in three patients and by surgery in 17 patients ( $p < 0.0015$ ). The groin haematomas in the endovascular treatment group did not require surgery while 14 neck haematomas in the surgery group did.

**Table 9.5 – CAVATAS: Outcome events within 30 days after treatment**

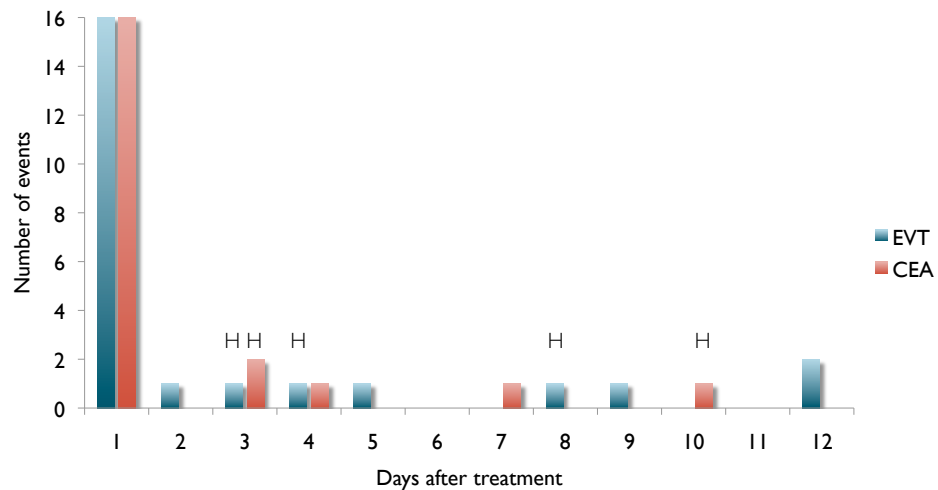
Data are number of patients (%). Stroke refers to events in any territory. None of the differences were statistically significant except for cranial nerve palsies ( $p < 0.0001$ ) and haematoma ( $p < 0.0015$ ). EVT, endovascular treatment; CEA, carotid endarterectomy.

|  | Intention to treat |                  | Per protocol     |                  |
|--|--------------------|------------------|------------------|------------------|
|  | EVT<br>(n = 251)   | CEA<br>(n = 253) | EVT<br>(n = 240) | CEA<br>(n = 246) |
| Fatal stroke   | 7<br>(3%)          | 1<br>(0.3%)      | 6<br>(3%)        | 1<br>(0.4%)      |
| Non-stroke death   | 0                  | 3<br>(2%)        | 0                | 3<br>(2%)        |
| Disabling stroke   | 9<br>(4%)          | 11<br>(4%)       | 9<br>(4%)        | 10<br>(4%)       |
| Non-disabling stroke lasting more than 7 days            | 9<br>(4%)          | 10<br>(4%)       | 9<br>(4%)        | 10<br>(4%)       |
| Non-disabling stroke lasting less than 7 days            | 8<br>(3%)          | 1<br>(0.3%)      | 8<br>(3%)        | 1<br>(0.4%)      |
| Disabling stroke or death                                | 16<br>(6%)         | 15<br>(6%)       | 15<br>(6%)       | 14<br>(6%)       |
| Stroke lasting more than 7 days or death                 | 25<br>(10%)        | 25<br>(10%)      | 24<br>(10%)      | 24<br>(10%)      |
| Cranial nerve palsy                                      | 0                  | 22<br>(9%)       | 0                | 22<br>(9%)       |
| Haematoma (requiring surgery or extending hospital stay) | 3<br>(1%)          | 17<br>(7%)       | 3<br>(1%)        | 17<br>(7%)       |
| Myocardial infarction                                    | 0                  | 3<br>(1%)        | 0                | 3<br>(1%)        |
| Pulmonary embolus  | 0                  | 2<br>(1%)        | 0                | 2<br>(1%)        |



**Figure 9.7 – CAVATAS: Timing and pathology of strokes lasting more than 7 days occurring within 12 days after treatment**

'H' represents a cerebral haemorrhage. Day 1 denotes the day of treatment.



#### *Efficacy*

All strokes occurring more than 30 days after first treatment were recorded as lasting longer than seven days. The number of outcome events are summarised in Table 9.4.

Any stroke or death occurred in 134 patients in the endovascular treatment group and in 131 patients in the surgery group. Stroke contributed to this outcome cluster 59 events in the endovascular group (14 fatal, 17 disabling, and 28 non-disabling) and 47 events (six fatal, 19 disabling, 22 non-disabling) in the surgery group.

The estimated 8-year cumulative incidence of any stroke or death was 54.4% (SE 4.0%) in the surgery group and 52.9% (SE 4.0%) in the endovascular group (Figure 9.8). The estimated hazard ratio including all available follow-up information was in favour of surgery, though not statistically significant (1.08, 95% CI 0.85 to 1.38, Figure 9.6).

Stroke of any duration or perioperative death occurred more often in patients allocated endovascular treatment (n = 67) than in patients allocated surgery (n = 51). After eight years, the cumulative incidence was 29.7% (SE 3.4%) in the endovascular treatment group and 23.5% (SE 3.5%) in the surgery group (Figure 9.9). No significant difference between

endovascular treatment and surgery was detected by the end of follow up (HR 1.35, 95% CI 0.94 to 1.93, Figure 9.6).

The 8-year estimated cumulative incidence of any stroke that lasted for more than 7 days or perioperative death was higher in the endovascular group (26.6%, SE 3.4%) than in the surgery group (23.1%, SE 3.5%, Figure 9.10) but the hazard ratio showed no significant difference between the groups (HR 1.19, 95% CI 0.82 to 1.72, Figure 9.6).

Non-perioperative stroke or TIA occurred in 67 patients in the endovascular group and 51 patients in the endarterectomy group. The 8-year cumulative incidence was higher in the endovascular group (36.9%, SE 5.0%) than in the surgery group (30.2%, SE 4.7%, Figure 9.11), but the estimated hazard ratio was not significantly different (HR 1.37, 95% CI 0.95 to 1.97, Figure 9.6).

Non-perioperative stroke occurred more frequently in the endovascular group than in the surgery group. The estimated 8-year cumulative incidence was 21.1% (SE 4.1%) in the former and 15.4% (SE 4.3%) in the latter group (Figure 9.12). However, this absolute risk reduction of 5.7% translating into a hazard ratio of 1.66 (95% CI 0.99 to 2.80) failed to reach statistical significance (Figure 9.6).

Ipsilateral stroke or TIA was more frequent in the endovascular treatment group compared to surgery ( $n = 34$  versus  $n = 27$ , respectively) and the 8-year estimated cumulative incidence was 19.3% (SE 4.0%) after endovascular treatment and 17.9% (SE 3.8%) after carotid endarterectomy (Figure 9.13). The hazard ratio showed no significant difference between the two treatments (HR 1.29, 95% CI 0.78 to 2.14, Figure 9.6).

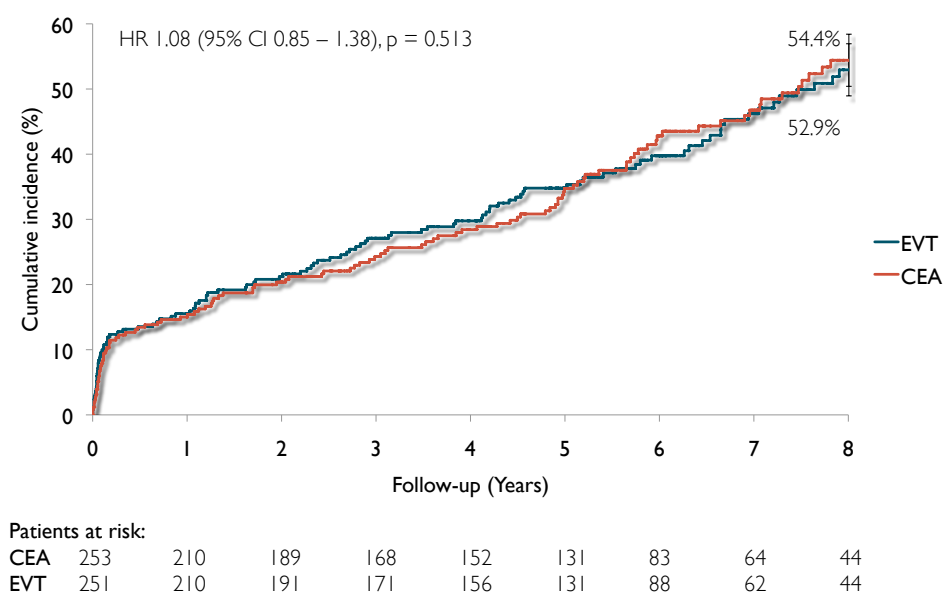
The 8-year cumulative incidence of ipsilateral stroke occurring more than 30 days after treatment was very similar in both groups. Eight years after randomisation, 11.3% (SE 3.7%) of patients in the endovascular treatment group had experienced an ipsilateral stroke compared to 8.6% (SE 3.1%) of patients in the surgery group (Figure 9.14). The increase in risk after endovascular treatment compared to surgery was not statistically significant (HR 1.22, 95% CI 0.59 to 2.54, Figure 9.6).

Contralateral stroke, i.e. stroke in a vascular territory other than that supplied by the randomised carotid artery, was almost twice as common following endovascular treatment (n = 24) than after surgery (n = 13) over the whole length of the trial but the estimated 8-year cumulative incidence of 11.6% (SE 2.5%) in the former and 11.2% (SE 4.2%) in the latter treatment group was almost identical (Figure 9.15). The hazard ratio calculated based on all available follow-up data showed an increased risk after endovascular treatment, albeit not a statistically significant one (HR 1.90, 95% CI 0.97 to 3.73, Figure 9.6).

It was mentioned above that death was the most commonly observed outcome event. By the end of follow-up 112 patients in the endovascular group and 118 patients in the surgery group had died. Almost half of patients had died by eight years of follow-up. The cumulative 8-year mortality was 43.0% (SE 4.0%) in the endovascular group and 48.6% (SE 4.2%) in the surgery group (Figure 9.16). The hazard ratio showed no significant difference between endovascular treatment and surgery (HR 1.07, 95% CI 0.82 to 1.40, Figure 9.6).

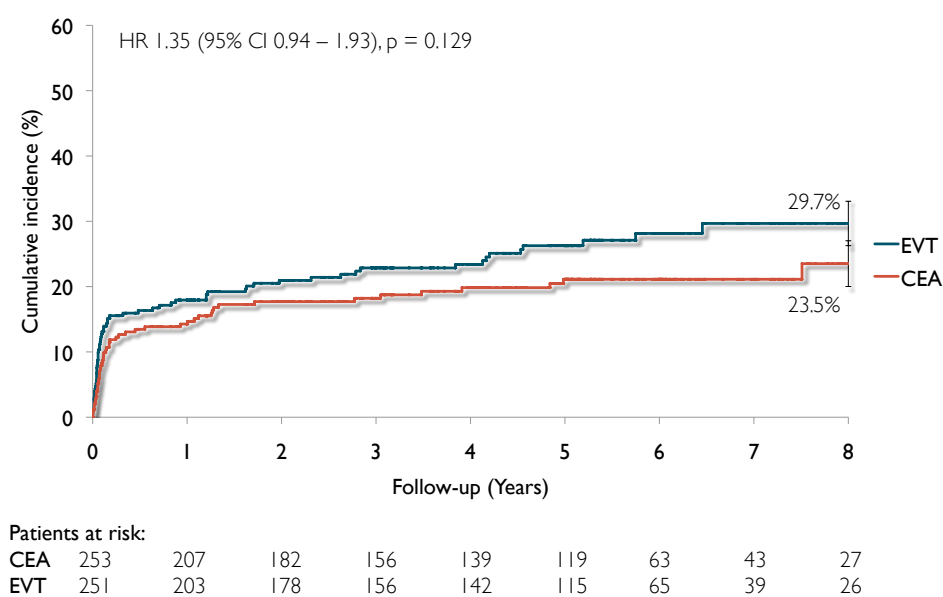
**Figure 9.8 – CAVATAS: 8-year cumulative incidence of stroke lasting more than 7 days or death (ITT)**

Shown is the Kaplan-Meier curve for any stroke or death up to 8 years after randomisation in the intention-to-treat analysis. The vertical bars represent the standard errors of the estimated 8-year cumulative incidence. EVT, endovascular treatment; CEA, carotid endarterectomy.



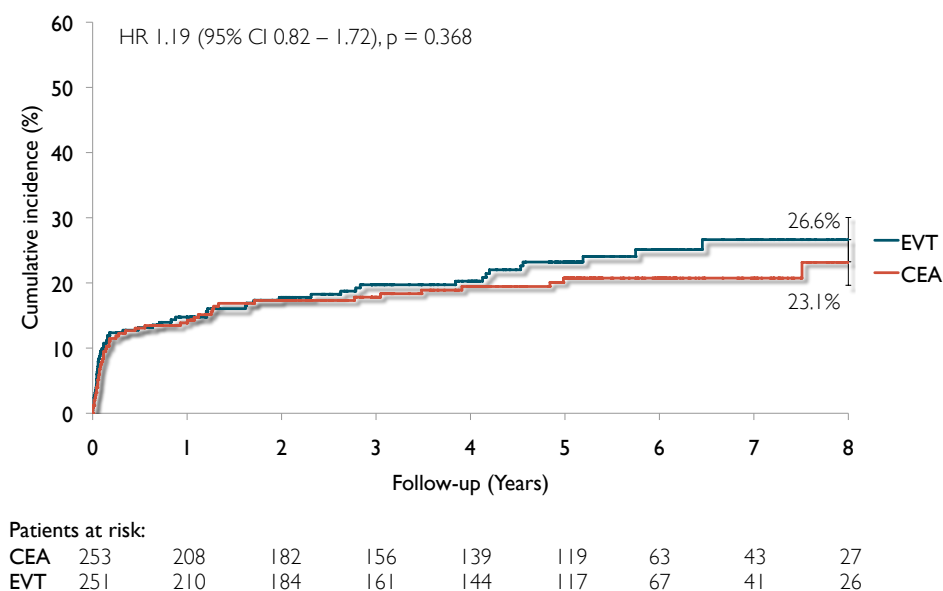
**Figure 9.9 – CAVATAS: 8-year cumulative incidence of any stroke or perioperative death (ITT)**

Shown is the Kaplan-Meier curve for any stroke or perioperative death up to 8 years after randomisation in the intention-to-treat analysis. The vertical bars represent the standard errors of the estimated 8-year cumulative incidence. EVT, endovascular treatment; CEA, carotid endarterectomy.



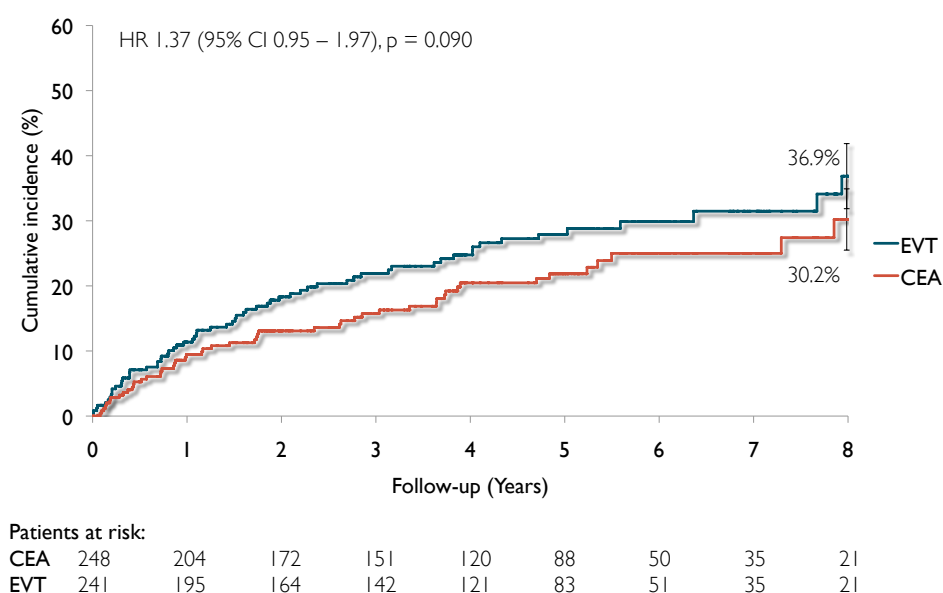
**Figure 9.10 – CAVATAS: 8-year cumulative incidence of stroke lasting more than 7 days or perioperative death (ITT)**

Shown is the Kaplan-Meier curve for stroke that lasted for more than 7 days or perioperative death up to 8 years after randomisation in the intention-to-treat analysis. The vertical bars represent the standard errors of the estimated 8-year cumulative incidence. EVT, endovascular treatment; CEA, carotid endarterectomy.



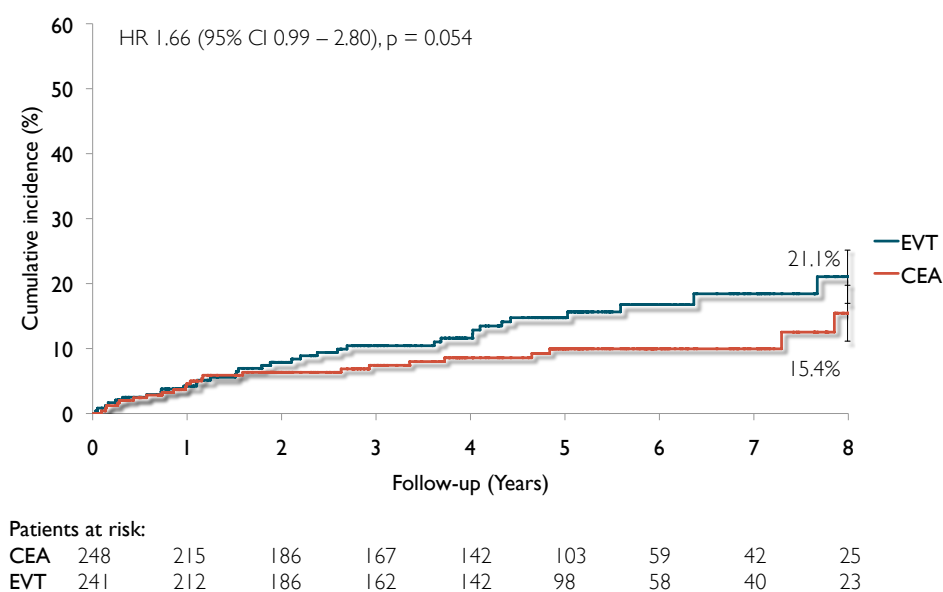
**Figure 9.11 – CAVATAS: 8-year cumulative incidence of non-perioperative stroke or TIA (ITT)**

Shown is the Kaplan-Meier curve for non-perioperative stroke or TIA up to 8 years after randomisation in the intention-to-treat analysis. The vertical bars represent the standard errors of the estimated 8-year cumulative incidence. EVT, endovascular treatment; CEA, carotid endarterectomy.



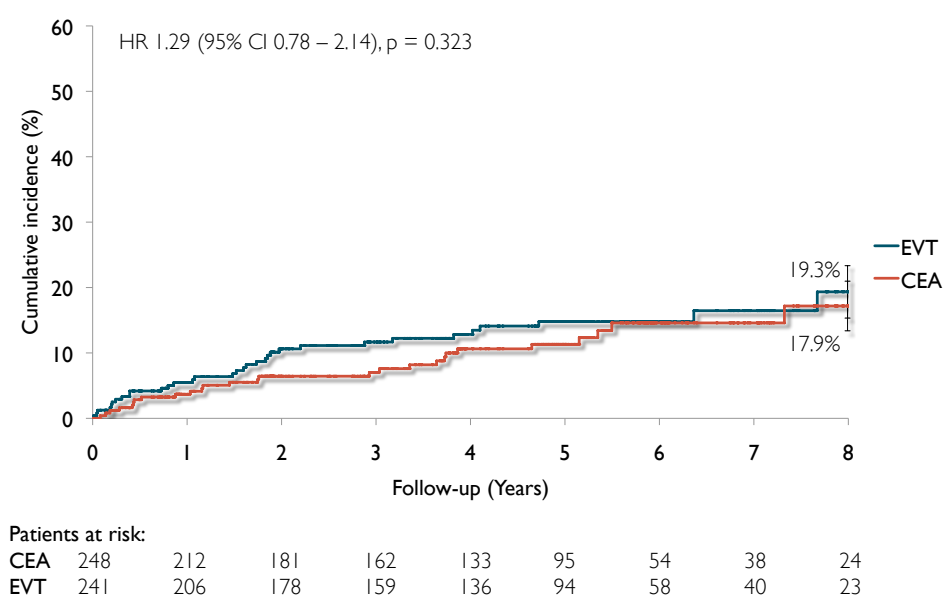
**Figure 9.12 – CAVATAS: 8-year cumulative incidence of non-perioperative stroke (ITT)**

Shown is the Kaplan-Meier curve for non-perioperative stroke up to 8 years after randomisation in the intention-to-treat analysis. The vertical bars represent the standard errors of the estimated 8-year cumulative incidence. EVT, endovascular treatment; CEA, carotid endarterectomy.



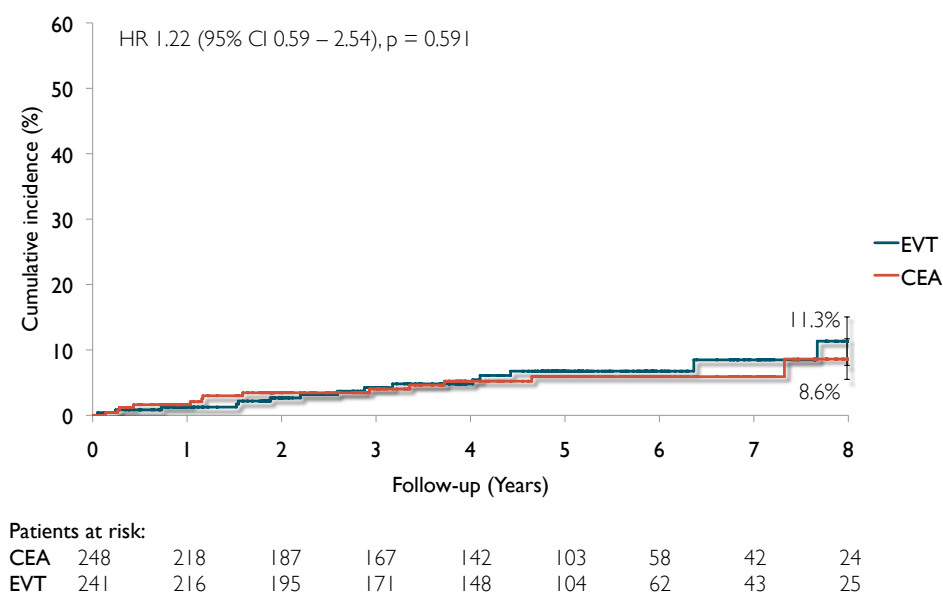
**Figure 9.13 – CAVATAS: 8-year cumulative incidence of ipsilateral non-perioperative stroke or TIA (ITT)**

Shown is the Kaplan-Meier curve for ipsilateral non-perioperative stroke or TIA up to 8 years after randomisation in the intention-to-treat analysis. The vertical bars represent the standard errors of the estimated 8-year cumulative incidence. EVT, endovascular treatment; CEA, carotid endarterectomy.



**Figure 9.14 – CAVATAS: 8-year cumulative incidence of ipsilateral non-perioperative stroke (ITT)**

Shown is the Kaplan-Meier curve for ipsilateral non-perioperative stroke up to 8 years after randomisation in the intention-to-treat analysis. The vertical bars represent the standard errors of the estimated 8-year cumulative incidence. EVT, endovascular treatment; CEA, carotid endarterectomy.



**Figure 9.15 – CAVATAS: 8-year cumulative incidence of contralateral non-perioperative stroke (ITT)**

Shown is the Kaplan-Meier curve for contralateral non-perioperative stroke up to 8 years after randomisation in the intention-to-treat analysis. The vertical bars represent the standard errors of the estimated 8-year cumulative incidence. EVT, endovascular treatment; CEA, carotid endarterectomy.

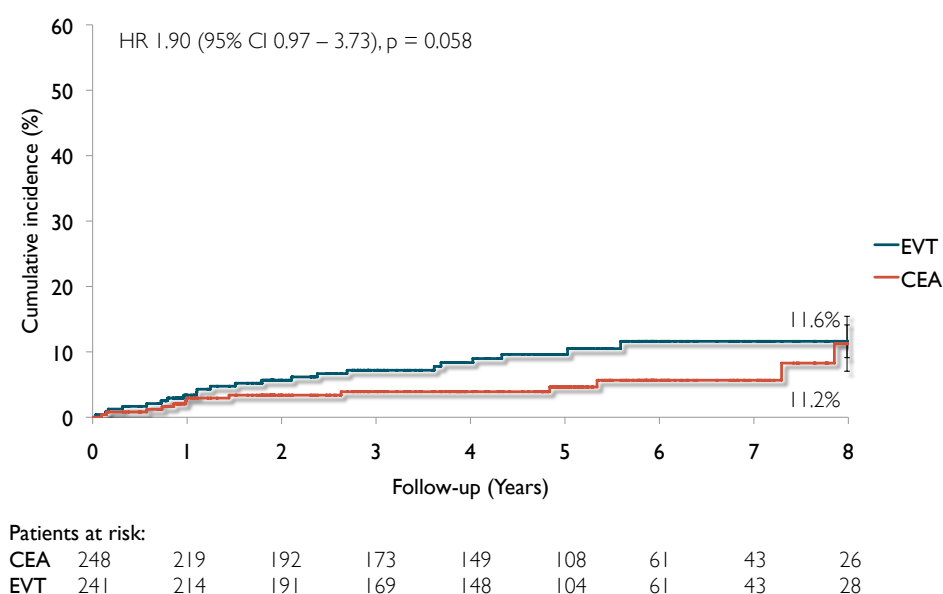
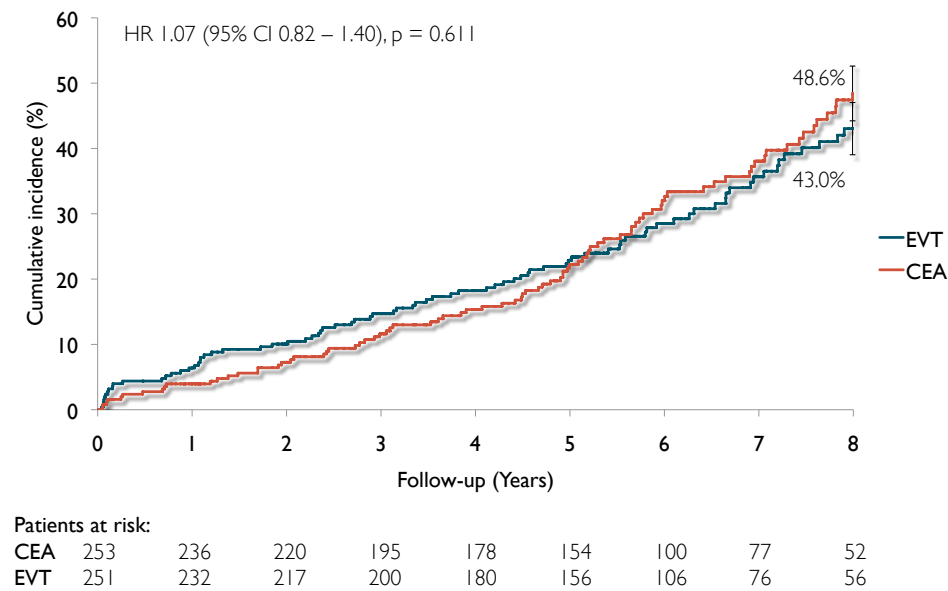


Figure 9.16 – CAVATAS: Mortality (ITT)

Shown is the Kaplan-Meier for death up to 8 years after randomisation in the intention-to-treat analysis. The vertical bars represent the standard errors of the estimated 8-year cumulative incidence. EVT, endovascular treatment; CEA, carotid endarterectomy.





## Per-protocol Analyses

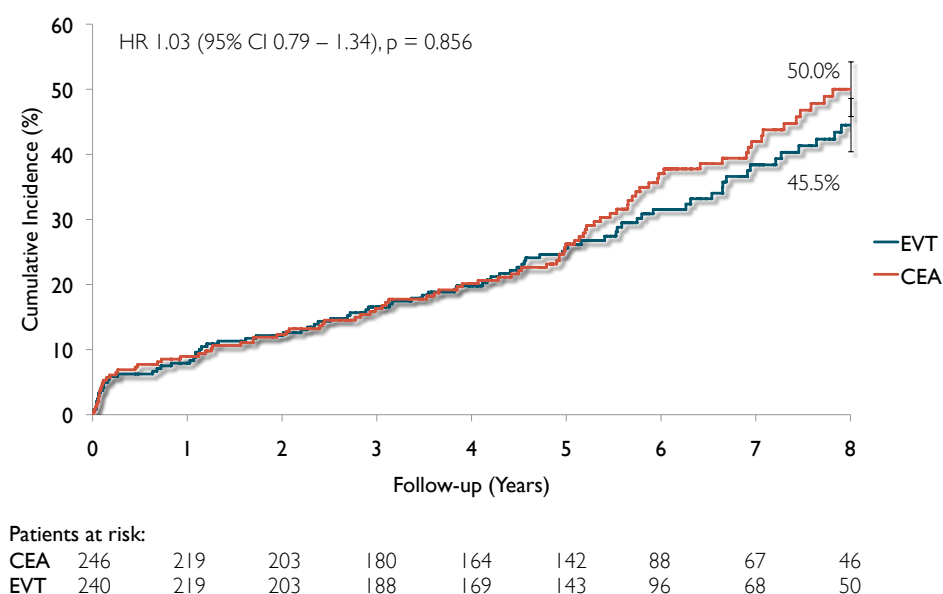
### Primary Outcome

The per-protocol analyses included only patients who received their allocated treatment. This was the case in 240 patients in the endovascular treatment group and 246 patients in the surgery group (see Table 9.4 for a summary of outcome events per treatment group).

The 8-year cumulative incidence of disabling stroke or death was higher after surgery (50.0%, SE 4.2%) than after endovascular treatment (45.5%, SE 4.1%, Figure 9.17), but the hazard ratio showed no significant difference between endovascular treatment and carotid endarterectomy (HR 1.03, 95% CI 0.79 to 1.34, Figure 9.18).

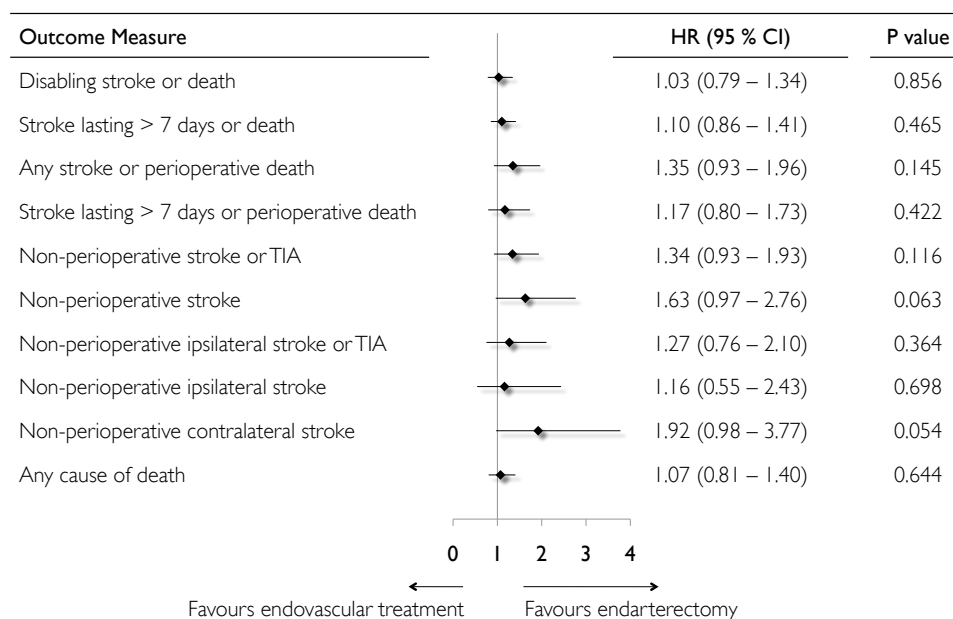
**Figure 9.17 – CAVATAS: 8-year cumulative incidence of disabling stroke or death (PP)**

Shown is the Kaplan-Meier curve for disabling stroke or death up to 8 years after randomisation in the per-protocol analysis. The vertical bars represent the standard errors of the estimated 8-year cumulative incidence. EVT, endovascular treatment; CEA, carotid endarterectomy.



**Figure 9.18 – CAVATAS: Hazard ratios for various outcome measures (PP)**

Hazard ratios (HR) are calculated based on the intention-to-treat data. CI, confidence interval.



### Efficacy

The estimated 8-year cumulative incidence of stroke that lasted for more than 7 days or death in patients who received the allocated carotid surgery was 54.2% (SE 4.1%). In patients who received the allocated endovascular treatment the incidence of any stroke or death was 52.6% (SE 4.1%, Figure 9.19). The estimated hazard ratio including all available follow-up information was 1.10 (95% CI 0.86 to 1.41) in favour of surgery (Figure 9.18).

Stroke of any duration or perioperative death was more common after endovascular treatment than after surgery. After 8 years, the cumulative incidence was 29.7% (SE 3.6%) in the endovascular treatment group and 21.9% (SE 3.1%) in the surgery group (Figure 9.20). This did not translate into a significant difference in risk (HR 1.35, 95% CI 0.93 to 1.96, Figure 9.18).

The 8-year estimated cumulative incidence of any stroke lasting more than 7 days or perioperative death was higher in the endovascular group (25.8%, SE 3.4%) than in the surgery group (22.6%, SE 3.6%, Figure 9.21) but the hazard ratio showed no significant difference between the groups (HR 1.17, 95% CI 0.80 to 1.73, Figure 9.18).

Restricting the analysis to cerebrovascular events occurring more than 30 days after treatment showed that non-perioperative stroke or TIA was more frequent in patients who received the allocated endovascular treatment than in those patients who received the allocated endarterectomy. The 8-year cumulative incidence was higher in the endovascular group (34.9%, SE 4.6%) than in the surgery group (30.9%, SE 4.9%, Figure 9.22), but the estimated hazard ratio was not significantly different (HR 1.34, 95% CI 0.93 to 1.93, Figure 9.18).

The per-protocol analysis of non-perioperative stroke alone showed no significant difference between endovascular treatment and carotid endarterectomy (HR 1.63, 95% CI 0.97 to 2.76, Figure 9.23), although the estimated 8-year cumulative incidence was higher in the former group (19.0%, SE 3.3% versus 15.8%, SE 4.4%, Figure 9.18).

In patients who received the allocated endovascular treatment, ipsilateral stroke or TIA was more frequent than in the patients who underwent the allocated carotid endarterectomy. The 8-year cumulative incidence was 17.5% (SE 3.9%) after endovascular treatment and 17.0% (SE 3.0%) after carotid endarterectomy (Figure 9.24). The hazard ratio showed no significant difference between the two treatments (HR 1.27, 95% CI 0.76 to 2.10, Figure 9.18).

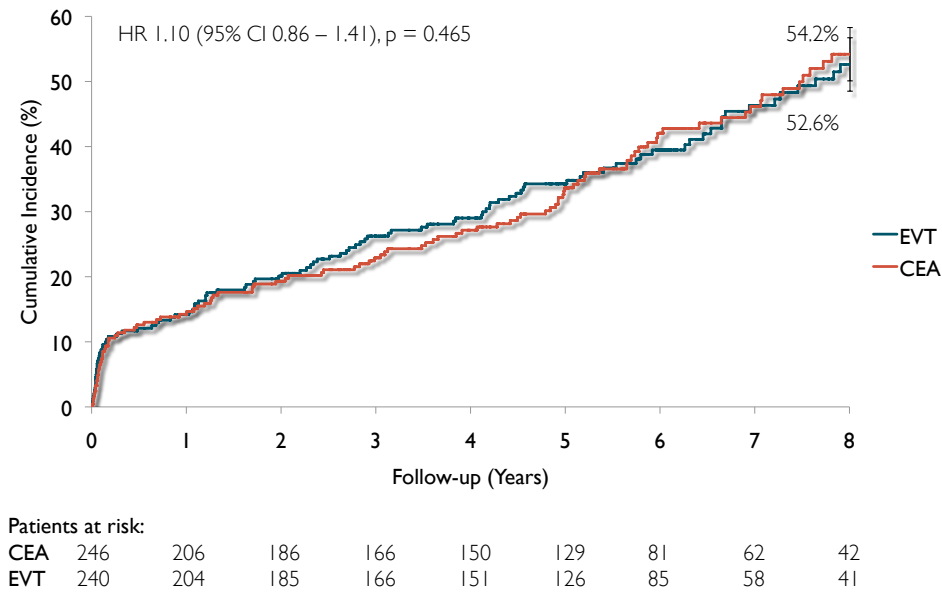
The 8-year cumulative incidence of ipsilateral stroke occurring more than 30 days after treatment was very similar in the patients undergoing the allocated endovascular treatment and carotid endarterectomy. After eight years, 8.7% (SE 2.6%) of patients allocated to and receiving endovascular treatment group had experienced an ipsilateral stroke compared to 8.9% (SE 3.3%) of patients in the surgery group (HR 1.16, 95% CI 0.55 to 2.43, Figure 9.18 and Figure 9.25).

The estimated 8-year cumulative incidence of non-perioperative stroke in a vascular territory other than that supplied by the randomised carotid artery was 12.0% (SE 2.5%) after endovascular treatment and 11.5% (SE 4.3%) after carotid surgery (Figure 9.26). The hazard ratio calculated based on all available follow-up showed an increased risk after endovascular treatment that approached statistical significance (HR 1.92, 95% CI 0.98 to 3.77, Figure 9.18).

The cumulative 8-year mortality was 42.2% (SE 4.2%) in the endovascular group and 48.1% (SE 4.3%) in the surgery group (Figure 9.27). The hazard ratio showed no significant difference between endovascular treatment and surgery (HR 1.07, 95% CI 0.81 to 1.40, Figure 9.18).

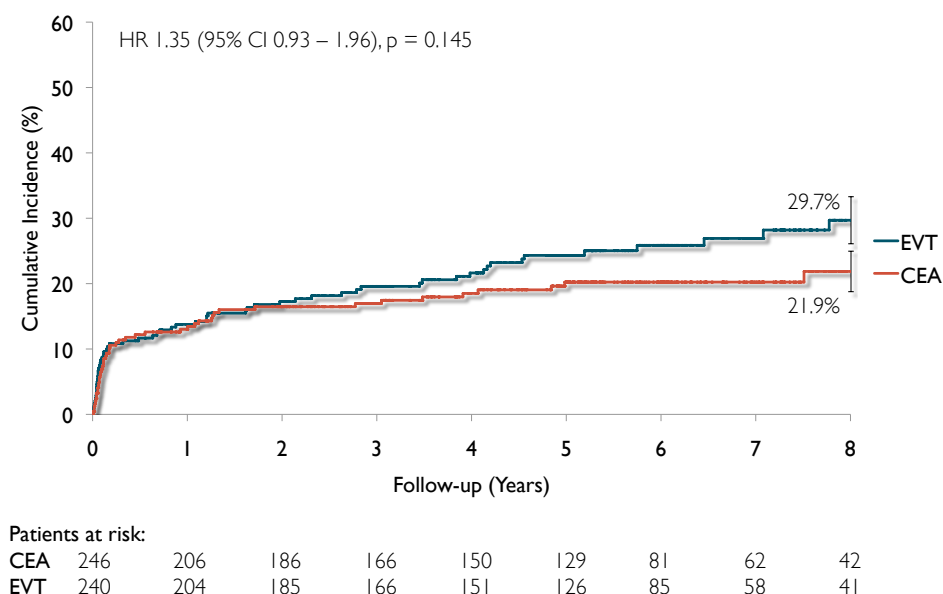
**Figure 9.19 – CAVATAS: 8-year cumulative incidence of stroke lasting more than 7 days or death (PP)**

Shown is the Kaplan-Meier curve for any stroke that lasted more than 7 days or death up to 8 years after randomisation in the per-protocol analysis. The vertical bars represent the standard errors of the estimated 8-year cumulative incidence. EVT, endovascular treatment; CEA, carotid endarterectomy.



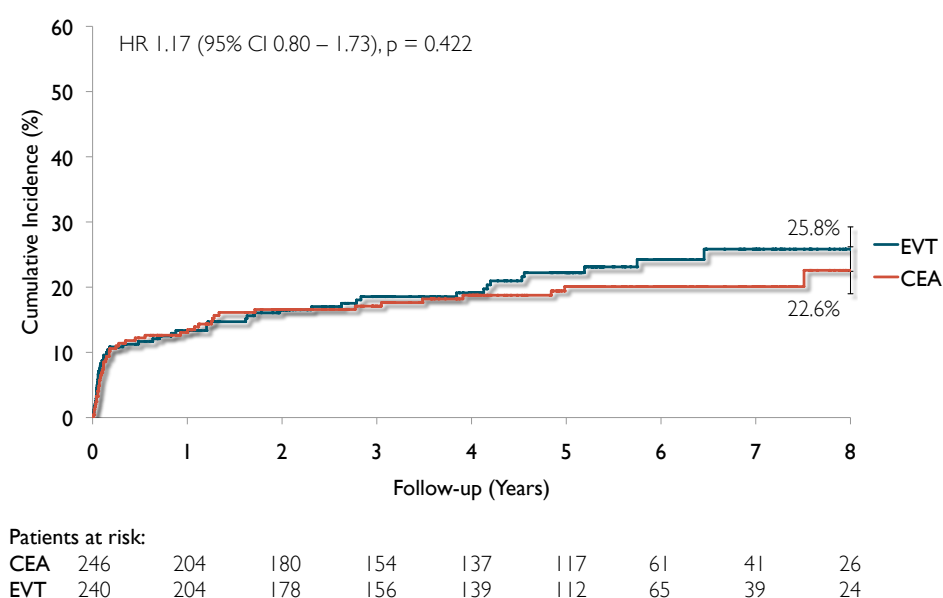
**Figure 9.20 – CAVATAS: 8-year cumulative incidence of any stroke or perioperative death (PP)**

Shown is the Kaplan-Meier curve for any stroke or perioperative death up to 8 years after randomisation in the per-protocol analysis. The vertical bars represent the standard errors of the estimated 8-year cumulative incidence. EVT, endovascular treatment; CEA, carotid endarterectomy.



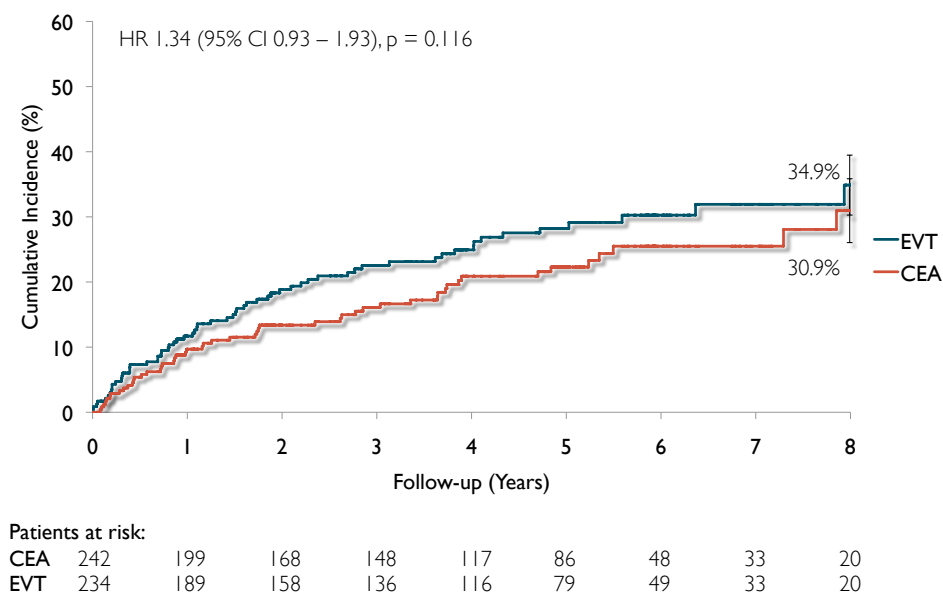
**Figure 9.21 – CAVATAS: 8-year cumulative incidence of stroke that lasted more than 7 days of perioperative death (PP)**

Shown is the Kaplan-Meier curve for stroke that lasted more than 7 days or perioperative death up to 8 years after randomisation in the per-protocol analysis. The vertical bars represent the standard errors of the estimated 8-year cumulative incidence. EVT, endovascular treatment; CEA, carotid endarterectomy.



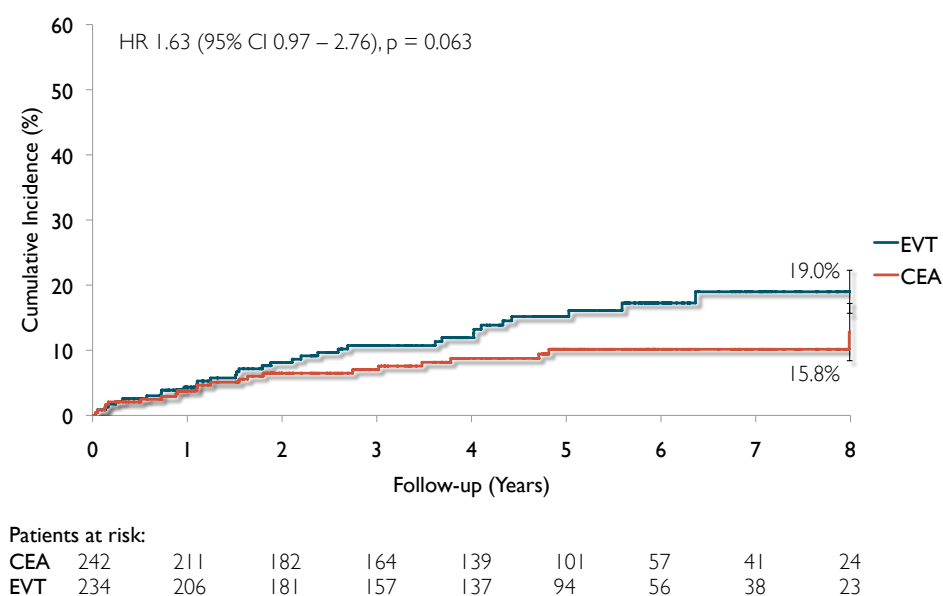
**Figure 9.22 – CAVATAS: 8-year cumulative incidence of non-perioperative stroke or TIA (PP)**

Shown is the Kaplan-Meier curve for non-perioperative stroke or TIA up to 8 years after randomisation in the per-protocol analysis. The vertical bars represent the standard errors of the estimated 8-year cumulative incidence. EVT, endovascular treatment; CEA, carotid endarterectomy.



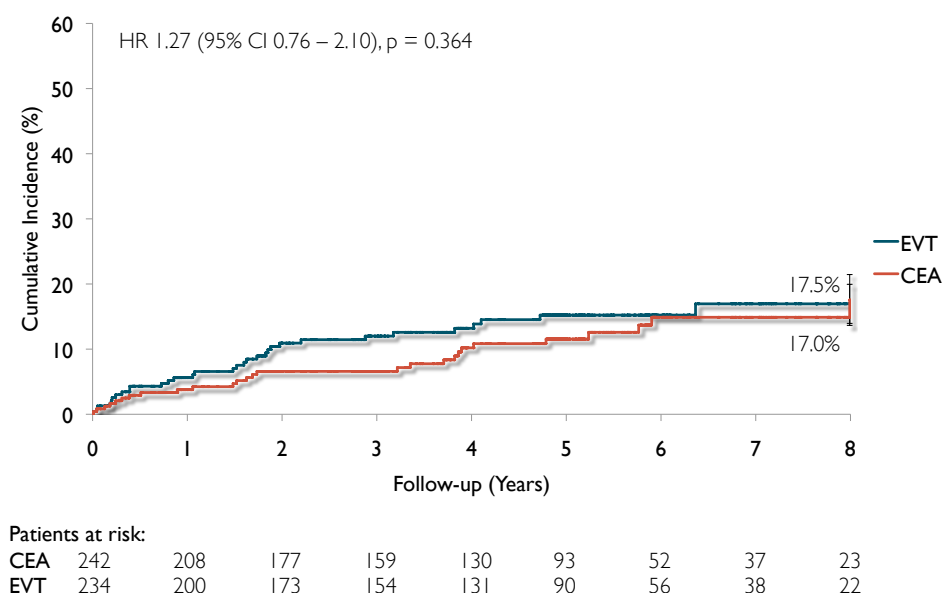
**Figure 9.23 – CAVATAS: 8-year cumulative incidence of non-perioperative stroke (PP)**

Shown is the Kaplan-Meier curve for non-perioperative stroke up to 8 years after randomisation in the per-protocol analysis. The vertical bars represent the standard errors of the estimated 8-year cumulative incidence. EVT, endovascular treatment; CEA, carotid endarterectomy.



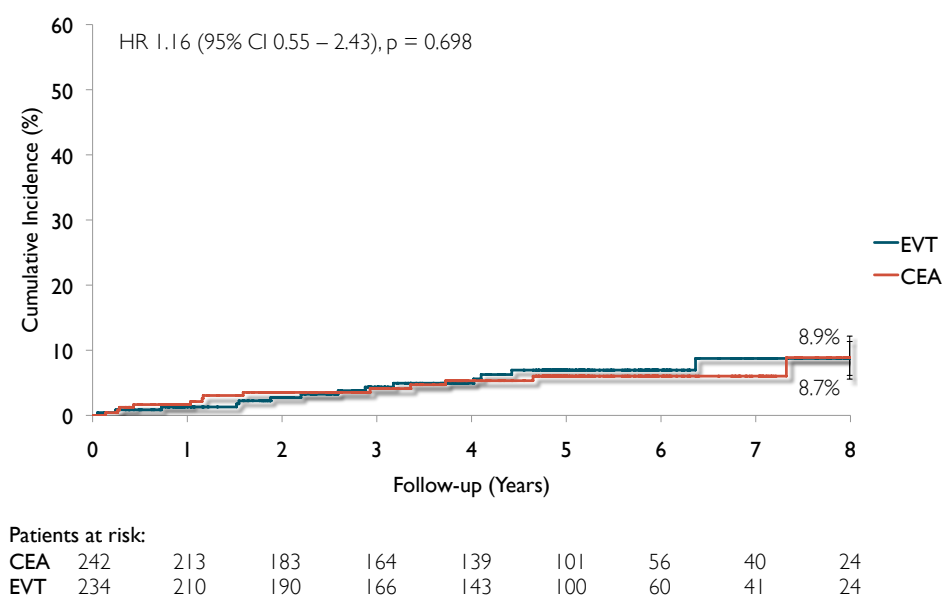
**Figure 9.24 – CAVATAS: 8-year cumulative incidence of ipsilateral non-perioperative stroke or TIA (PP)**

Shown is the Kaplan-Meier curve for ipsilateral non-perioperative stroke or TIA up to 8 years after randomisation in the per-protocol analysis. The vertical bars represent the standard errors of the estimated 8-year cumulative incidence. EVT, endovascular treatment; CEA, carotid endarterectomy.



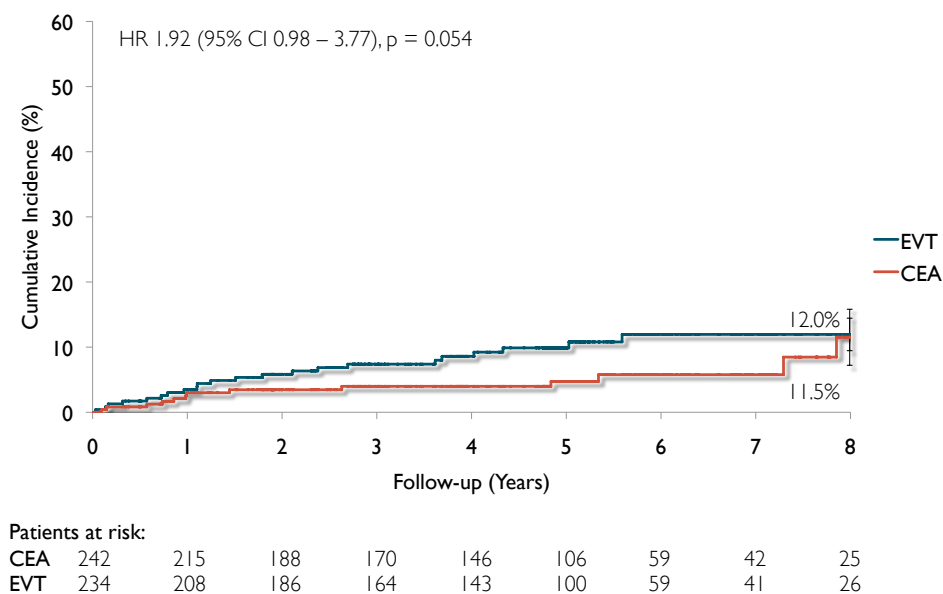
**Figure 9.25 – CAVATAS: 8-year cumulative incidence of ipsilateral non-perioperative stroke (PP)**

Shown is the Kaplan-Meier curve for ipsilateral non-perioperative stroke up to 8 years after randomisation in the per-protocol analysis. The vertical bars represent the standard errors of the estimated 8-year cumulative incidence. EVT, endovascular treatment; CEA, carotid endarterectomy.



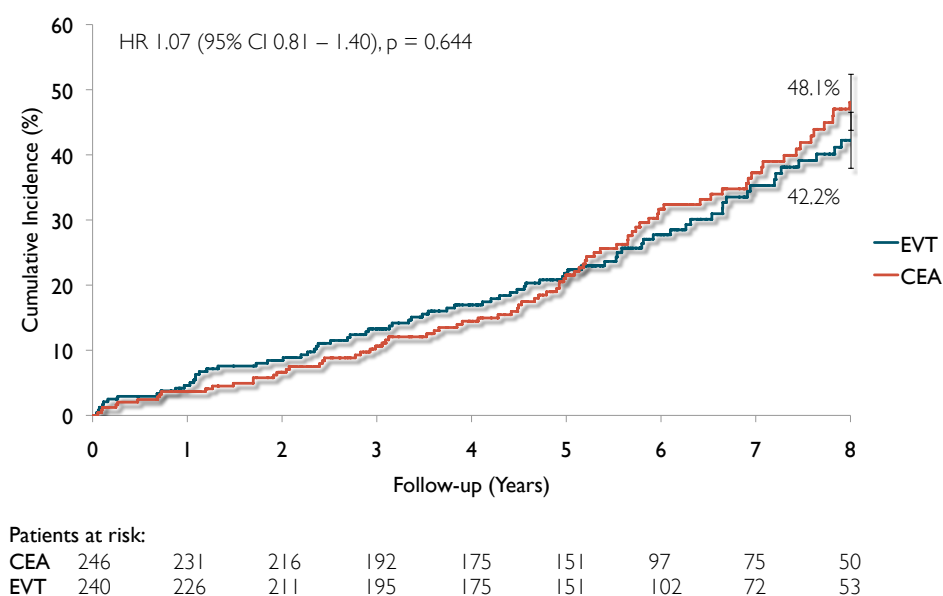
**Figure 9.26 – CAVATAS: 8-year cumulative incidence of contralateral non-perioperative stroke (PP)**

Shown is the Kaplan-Meier curve for any stroke or perioperative death up to 8 years after randomisation in the per-protocol analysis. The vertical bars represent the standard errors of the estimated 8-year cumulative incidence. EVT, endovascular treatment; CEA, carotid endarterectomy.



**Figure 9.27 – CAVATAS: Mortality (PP)**

Shown is the Kaplan-Meier curve for death up to 8 years after randomisation in the per-protocol analysis. The vertical bars represent the standard errors of the estimated 8-year cumulative incidence. EVT, endovascular treatment; CEA, carotid endarterectomy.



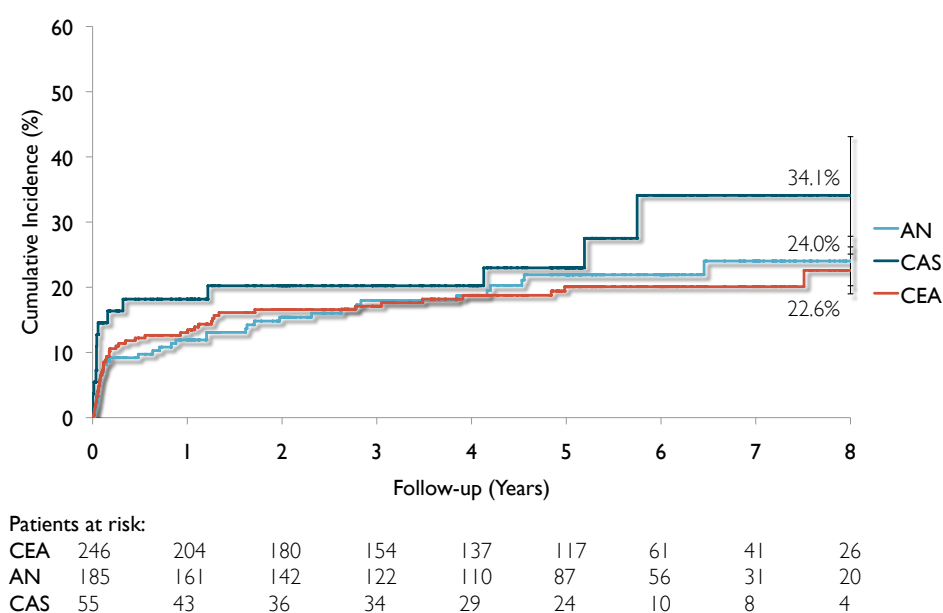


## Subgroup analyses

The majority of patients assigned to endovascular treatment were treated by angioplasty alone. Only 55 patients (22.5%) of those who received the allocated endovascular treatment underwent stenting and 185 patients were treated with balloon angioplasty alone. The 8-year cumulative incidence of stroke lasting more than seven days or perioperative death was highest in the patients who received a stent (34.1%, SE 9.0%, Figure 9.28). Patients who were treated with balloon angioplasty alone had an 8-year cumulative incidence of stroke lasting more than seven days or perioperative death of 24.0% (SE 3.8%) and surgically treated patients a risk of 22.6% (SE 3.6 5).

**Figure 9.28 – CAVATAS: 8-year cumulative incidence of stroke that lasted more than 7 days or perioperative death (PP)**

Shown is the Kaplan-Meier curve for stroke that lasted for more than 7 days or perioperative death up to 8 years after randomisation in the per-protocol analysis. Patients allocated to endovascular treatment are divided into those receiving stenting and those undergoing balloon angioplasty alone. The vertical bars represent the standard errors of the estimated 8-year cumulative incidence. AN, balloon angioplasty; CAS, carotid stenting; CEA, carotid endarterectomy.



The higher risk of stenting compared to balloon angioplasty did not reach statistical significance in the within-subgroup analysis (HR 1.37, 95% CI 0.74 to 2.52). Compared to surgery, the higher risk of stenting was also not statistically significant (HR 1.41, 95% CI 0.78 to 2.56).

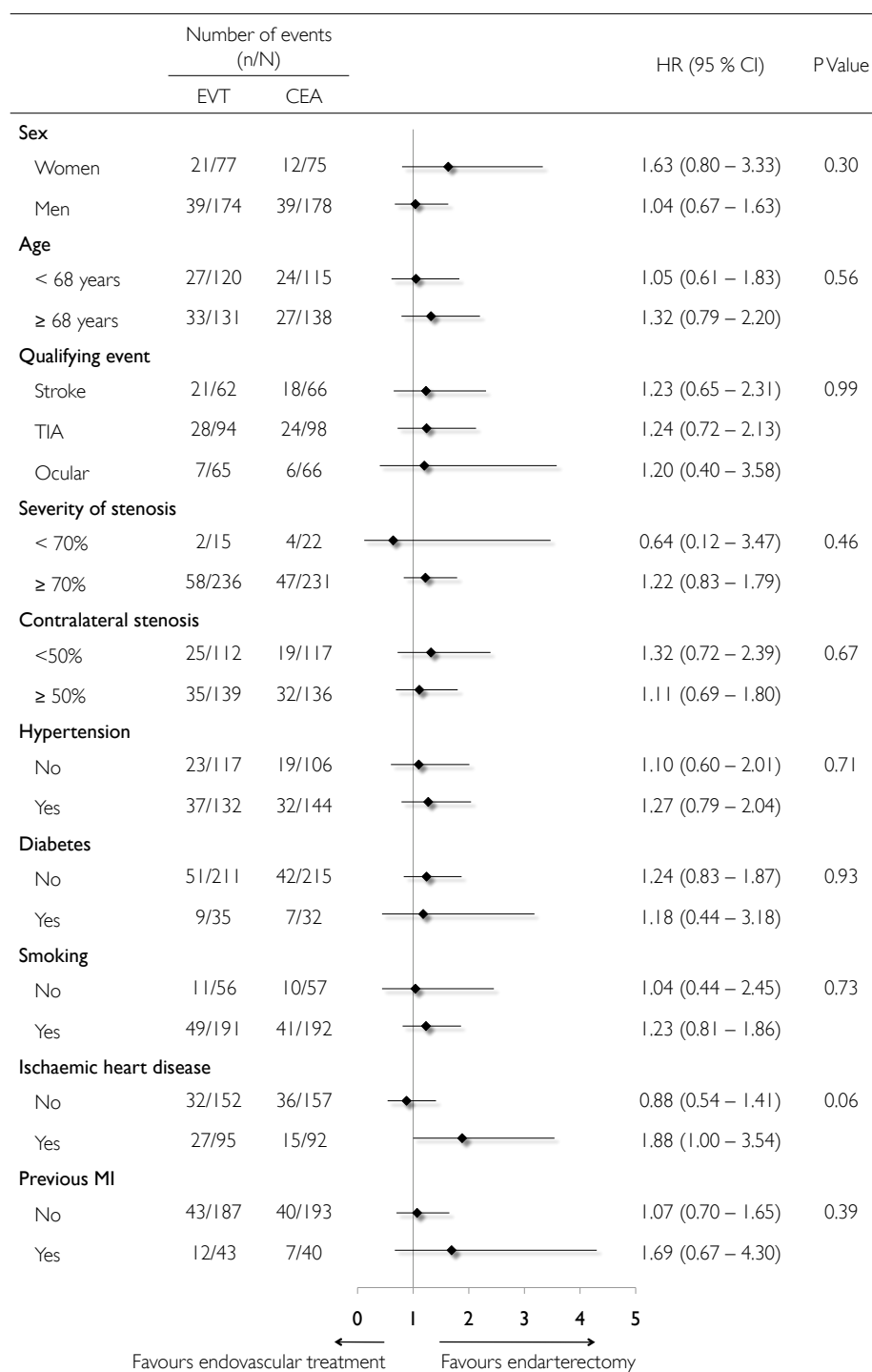
The exploratory subgroup analyses examining the influence of baseline variables on the long-term rate of stroke lasting more than seven days or perioperative death showed no significant interaction with treatment effect of any of the variables tested (Figure 9.29).

The risk of stroke lasting more than seven days or perioperative death after endovascular treatment in patients younger than 68 years appeared to be similar to the risk in patients undergoing surgery (HR 1.05, 95% CI 0.61 to 1.83) but there was a trend in favour of surgery in those patients older than 68 years (HR 1.32, 95% CI 0.79 to 2.20).

In patients with ischaemic heart disease at time of randomisation there was also a strong trend in favour of endarterectomy over endovascular treatment (HR 1.88, 95% CI 1.00 to 3.54).

**Figure 9.29 – CAVATAS: Subgroup analyses to compare the rates of the outcome event of stroke in territory that lasted more than 7 days or perioperative death, according to various baseline characteristics**

*P* values are associated with treatment-covariate interaction tests. Analyses are by intention to treat. N, number of patients in each group; n, number of events; EVT, endovascular treatment; CEA, carotid endarterectomy; HR, hazard ratio; TIA, transient ischaemic attack; MI, myocardial infarction.



## Restenosis

In 200 patients who completed endovascular treatment and 213 patients who completed carotid endarterectomy ultrasound follow-up was available for analysis (median follow-up 4 years, Table 9.6). The ultrasound criteria are summarised in Table 8.1, page 56.

**Table 9.6 – CAVATAS restenosis study: Patient characteristics at baseline per allocated treatment**

Data are number of patients (% of known data), unless otherwise indicated. EVT, endovascular treatment; CEA, carotid endarterectomy; SD, standard deviation; IQR, interquartile range.

|   | EVT<br>(n = 200) | CEA<br>(n = 213) |
|---|------------------|------------------|
| Age (mean [SD], years)  | 67 [8.5]         | 67 [8.3]         |
| Sex   |                  |                  |
| Women   | 48 (29%)         | 69 (32%)         |
| Men   | 142 (71%)        | 144 (68%)        |
| Vascular risk factors   |                  |                  |
| Hypertension  | 103 (52%)        | 121 (57%)        |
| Diabetes mellitus   | 28 (14%)         | 29 (14%)         |
| Cholesterol > 6.5 mmol/L  | 53 (27%)         | 54 (25%)         |
| Smokers, past or present  | 151 (76%)        | 156 (73%)        |
| Prior history of cardio-/cerebrovascular disease                        |                  |                  |
| Ischaemic heart disease   | 78 (39%)         | 77 (36%)         |
| Peripheral vascular disease   | 42 (21%)         | 44 (21%)         |
| Ipsilateral cerebrovascular events within 6 months before randomisation | 192 (96%)        | 202 (95%)        |
| Degree of ipsilateral carotid stenosis (mean [SD])                      | 77 [14.2]        | 77 [14.5]        |

Restenosis  $\geq 70\%$  occurred significantly more often in patients randomised to endovascular treatment (n = 53) compared to patients randomised to surgery (n = 20). Restenosis occurred within the first year after treatment in the majority of cases. One year after treatment, the cumulative incidence of stenosis  $\geq 70\%$  was 21.7% (SE 3.0%) in

the endovascular treatment arm and 7.5% (SE 1.9%) in the surgery arm. Five years after treatment, the cumulative incidence of carotid restenosis  $\geq 70\%$  was 30.7% (SE 3.7%) after endovascular treatment and 10.5% (SE 2.4%) after surgery (HR 3.17, 95% CI 1.89 to 5.32,  $p < 0.0001$ , Table 9.7 and Figure 9.30).

Restenosis  $\geq 50\%$  was also more frequent in the endovascular treatment group compared to surgery (109 *versus* 59 patients, respectively). One year after treatment the cumulative incidence of this outcome was 48.5% (SE 3.6%) in the endovascular treatment group and 20.7% (SE 2.9%) in the surgery group. After 5 years the cumulative incidence had increased to 58.6% (SE 3.9%) after endovascular treatment and to 31.5% (SE 3.5%) after surgery (HR 2.58, 95% CI 1.87 to 3.55,  $p < 0.0001$ , Figure 9.30).

Patients receiving a stent had a lower risk of developing  $\geq 50\%$  stenosis (HR 0.37, 95% CI 0.21 to 0.62,  $p = 0.0003$ ) and  $\geq 70\%$  stenosis than patients undergoing balloon angioplasty alone (HR 0.43, 95% CI 0.19 to 0.97,  $p = 0.042$ , Figure 9.31).

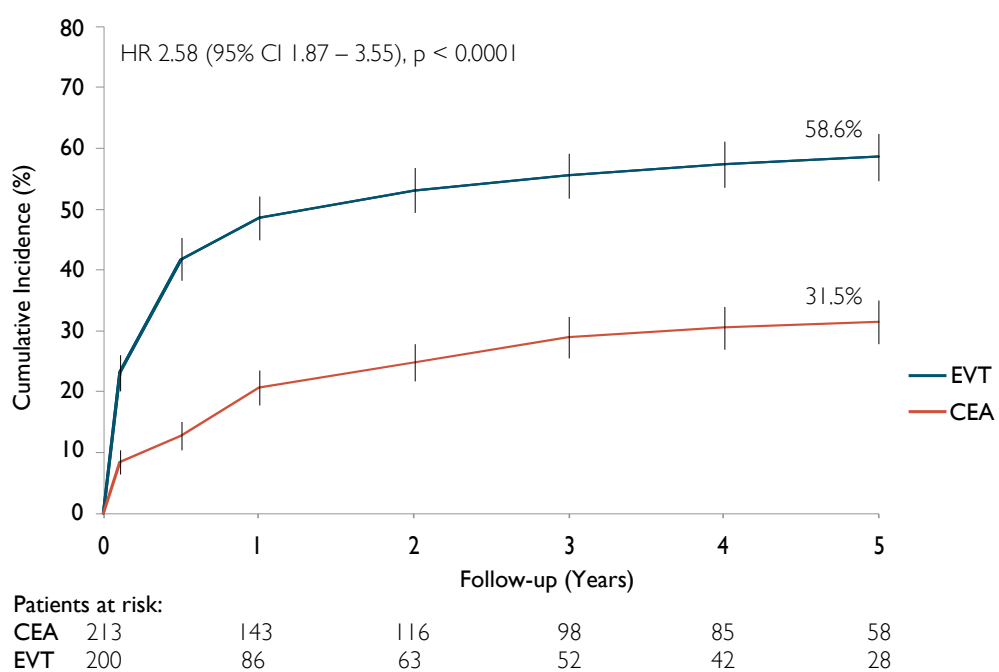
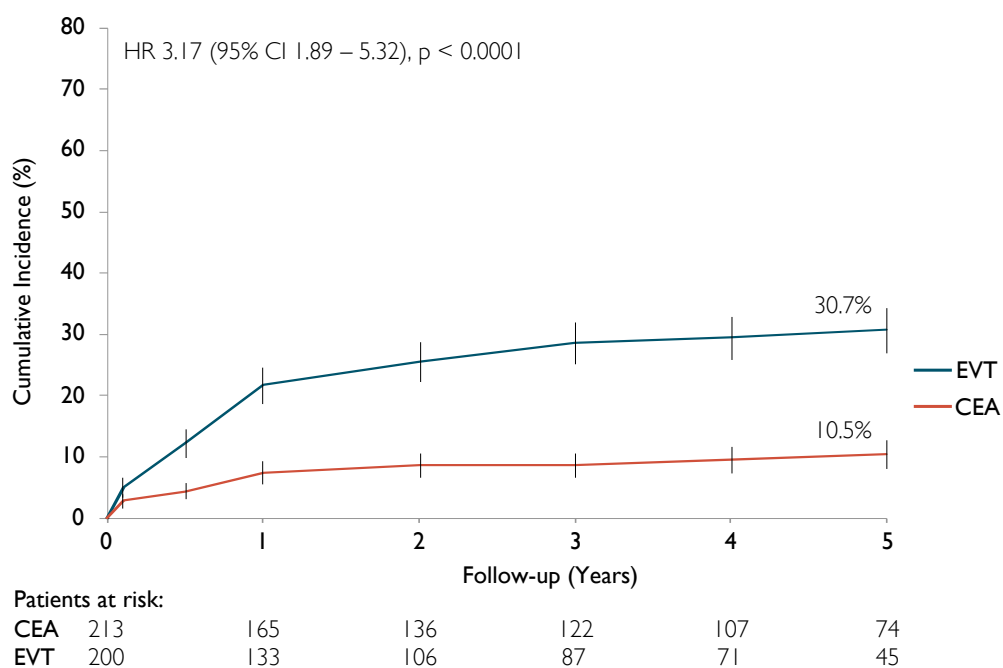
**Table 9.7 – CAVATAS: Carotid restenosis or occlusion after treatment**

Data are number of patients. Numbers in brackets indicate contribution of individual outcomes to the composite endpoint. All non-perioperative strokes lasted for more than 7 days. EVT, endovascular treatment; AN, balloon angioplasty; CAS, carotid stenting; CEA, carotid endarterectomy.

| Intention to treat   |                    |                       | Per protocol (endovascular treatment only) |                    |                       |
|--|--------------------|-----------------------|--|--------------------|-----------------------|
| EVT<br>(n = 200)   | CEA<br>(n = 213)   | HR (95% CI)           | CAS<br>(n = 50)                            | AN<br>(n = 145)    | HR (95% CI)           |
| <b>Restenosis <math>\geq 70\%</math> or occlusion</b> (1-year cumulative incidence, 5-year cumulative incidence) |                    |                       |  |                    |                       |
| 53<br>(21.7, 30.7)   | 20<br>(7.5, 10.5)  | 3.17<br>(1.89 – 5.32) | 7<br>(13.1, 16.6)                          | 46<br>(25.3, 36.2) | 0.43<br>(0.19 – 0.97) |
| <b>Restenosis <math>\geq 50\%</math> or occlusion</b>  |                    |                       |  |                    |                       |
| 109<br>(48.5, 58.6)  | 59<br>(20.7, 31.5) | 2.58<br>(1.87 – 3.55) | 16<br>(23.0, 36.6)                         | 93<br>(58.8, 68.1) | 0.37<br>(0.21 – 0.62) |

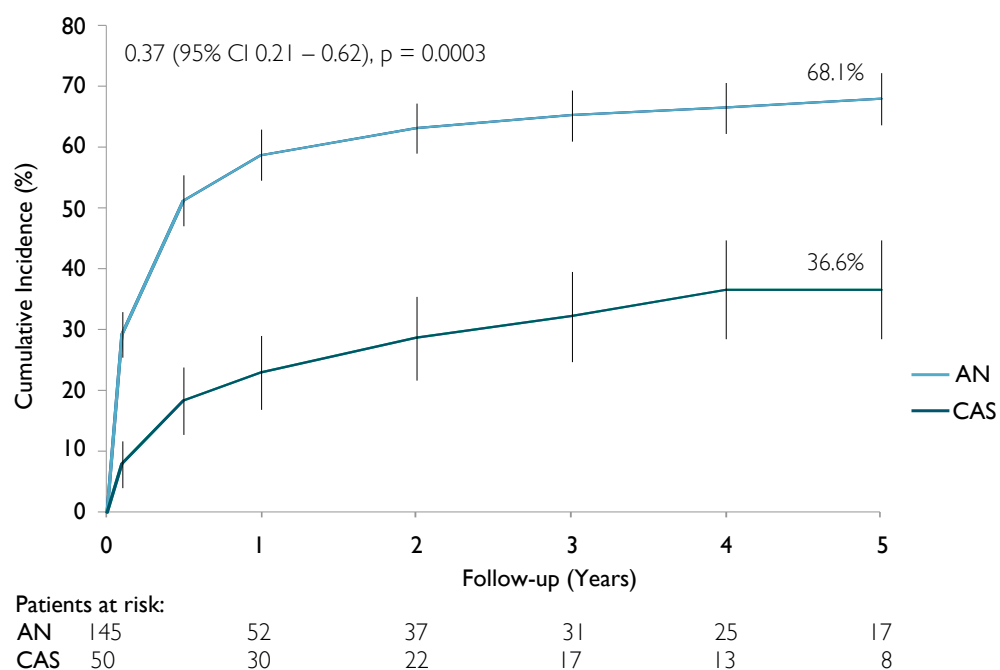
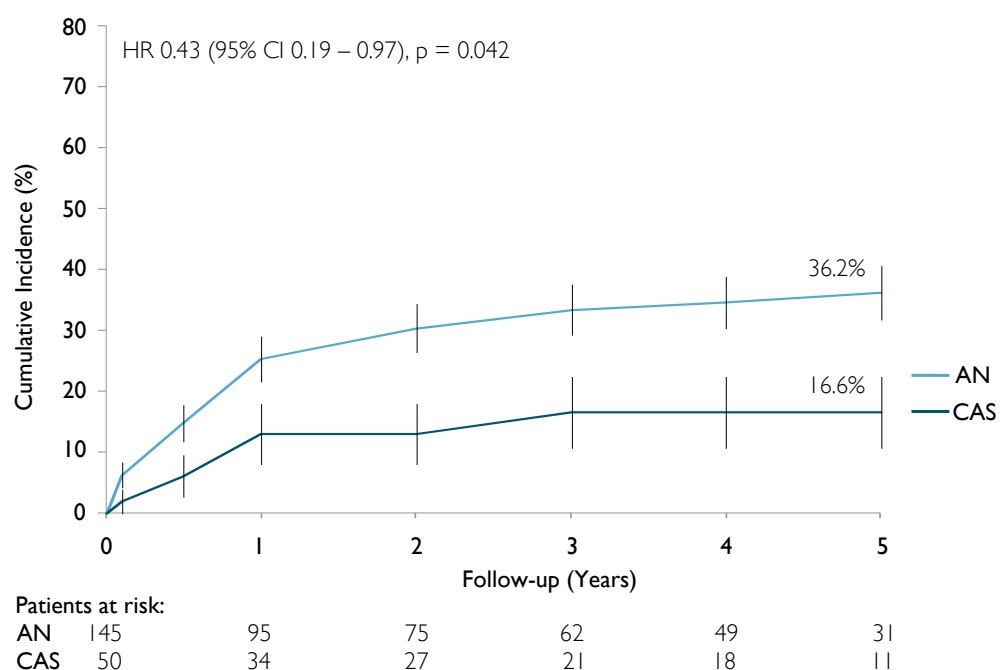
**Figure 9.30 – CAVATAS: 5-year cumulative incidence of carotid restenosis**

Shown is the cumulative incidence of restenosis  $\geq 70\%$  (upper graph) and  $\geq 50\%$  (lower graph) using life-table analysis. EVT, endovascular treatment; CEA, carotid endarterectomy.



**Figure 9.31 – CAVATAS: 5-year cumulative incidence of restenosis in patients allocated to endovascular treatment**

Shown is the cumulative incidence of restenosis  $\geq 70\%$  (upper graph) and  $\geq 50\%$  (lower graph) using life-table analysis. AN, balloon angioplasty; CAS, carotid stenting.



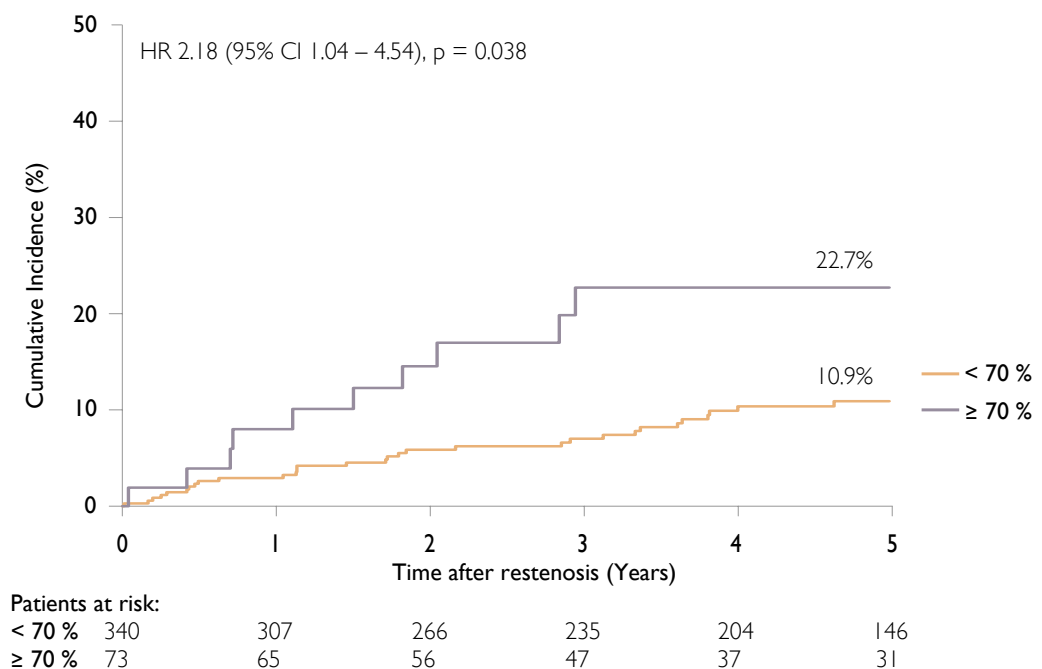
Smoking at the time of randomisation or in the past independently predicted restenosis  $\geq 70\%$  (HR 2.32, 95% CI 1.19 to 4.54,  $p = 0.014$ ) without significant interaction between smoking history and allocated treatment.

Recurrent or residual stenosis between 50 and 69% within 60 days after treatment was associated with a significant increase in the risk of the stenosis progressing to  $\geq 70\%$  (HR 3.76, 95% CI 1.88 to 7.52,  $p = 0.0002$ ).

In turn, Restenosis  $\geq 70\%$  diagnosed within the first year after treatment carried a higher risk of ipsilateral non-perioperative stroke or TIA. The 5-year cumulative incidence was 22.7% in patients with  $\geq 70\%$  stenosis compared to 10.9% with less than 70% stenosis (HR 2.18, 95% CI 1.04 to 4.54,  $p = 0.038$ , Figure 9.32).

**Figure 9.32 – CAVATAS restenosis study: 5-year cumulative incidence of ipsilateral stroke or TIA**

Shown is the Kaplan-Meier cumulative incidence of ipsilateral stroke or TIA during 5 years of follow-up in patients with 70% or more restenosis in the first year after treatment compared with patients with less than 70% restenosis in the first year after treatment. Time is from the first ultrasound examination done within the first year after treatment that confirmed restenosis.

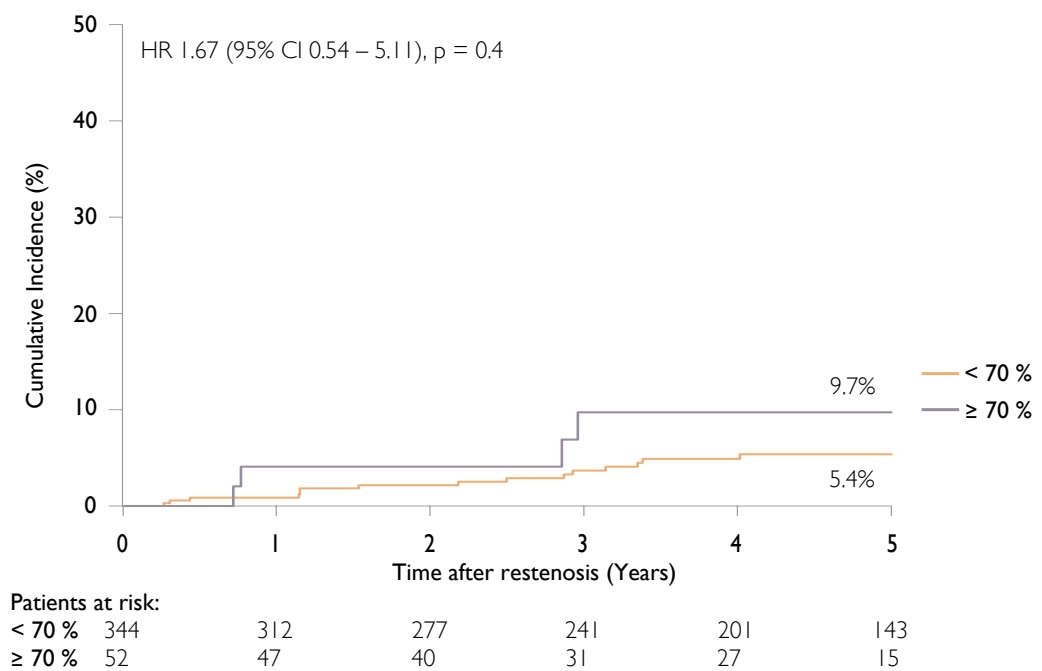




The 5-year risk of ipsilateral stroke was also greater in patients with at least 70% restenosis (9.7% *versus* 5.4%, although it did not reach statistical significance (HR 1.67, 95% CI 0.54 to 5.11,  $p = 0.4$ , Figure 9.33).

**Figure 9.33 – CAVATAS restenosis study: 5-year cumulative incidence of ipsilateral stroke**

Shown is the Kaplan-Meier cumulative incidence of ipsilateral stroke or TIA during 5 years of follow-up in patients with 70% or more restenosis in the first year after treatment compared with patients with less than 70% restenosis in the first year after treatment. Time is from the first ultrasound examination done within the first year after treatment that confirmed restenosis.



### 9.2.3 Discussion

CAVATAS was the first large randomised clinical trial comparing endovascular treatment and carotid endarterectomy for mainly symptomatic carotid stenosis. It addressed two main questions concerning endovascular treatment of atherosclerotic carotid artery stenosis.

The primary outcome measure defined as disabling stroke or death reflected the main aim of the trial to provide data on the long-term effectiveness of endovascular treatment compared to surgery and inform on the value of treatment to the patient and the health service. The trial showed a very small and non-significant increase in risk of disabling

stroke or death over the whole course of the trial in the endovascular treatment group compared to the surgery group. The majority of events contributing to this outcome cluster were non-stroke-related deaths (72% in the endovascular group and 77% in the surgery group). The number of disabling strokes was virtually identical, but more than twice as many patients in the endovascular group suffered a fatal stroke than patients in the surgery group. NASCET only reported risks up to five years after randomisation (Barnett *et al.* 1998). The 5-year rate of disabling stroke or death of any cause after carotid endarterectomy reported there was 18.3% and thus slightly higher than the 5-year risk of 16.5% following endovascular treatment and 17.5% following carotid endarterectomy in CAVATAS.

Since non-stroke-related mortality dominated the primary outcome cluster, excluding long-term mortality that is not directly attributable to stroke may provide a better estimate of the long-term effectiveness of endovascular treatment and surgery. The risk of any stroke or perioperative death was also higher in the endovascular group than in the surgery group but the difference in risk failed to reach statistical significance (HR 1.35, 95% CI 0.94 to 1.93).

The CAVATAS steering committee had decided prospectively to exclude stroke that lasted for fewer than seven days from the analysis of short-term outcome data. There was concern that minor short-lived events were more likely to be detected in patients who were returned to a neurological ward and looked after by a team trained in diagnosing stroke, as it was mainly the case in patients undergoing endovascular treatment. Surgical patients were generally returned to an intensive care setting before moving to a surgical ward. Moreover, ECST, the European benchmark for CAVATAS at the time the trial was initiated had also excluded minor stroke from its analysis (Farrell *et al.* 1998). The incidence of minor procedural strokes that lasted for fewer than seven days was analysed for the first time for this thesis and the associated publications (Bonati *et al.* 2009; Ederle *et al.* 2009a). Non-disabling stroke lasting less than seven days was more frequent in the endovascular group compared to surgery (eight *versus* one event,

respectively). Notable is the fact that all non-disabling stroke that lasted for fewer than seven days occurred within 30 days of the procedure. All strokes occurring more than 30 days after treatment reported to the central trial office lasted for more than seven days. This finding of excess in minor strokes in the endovascular treatment group is not necessarily because of an underreporting in the surgery group as the Trial Steering Committee envisaged it. Six out of eight non-disabling strokes that lasted for fewer than seven days in the endovascular treatment group occurred on the day of treatment and it is possible that manipulation of the stenosis with the angioplasty equipment caused some sort of instability in the plaque that directly led to a minor stroke.

ECST has published long-term results and reported a 10-year risk of ipsilateral stroke after carotid endarterectomy of 9.7% (Cunningham *et al.* 2002). This is similar to the 8-year risk of 8.6% following surgery and 11.3% after endovascular treatment found in CAVATAS.

Neither the primary outcome nor any of the secondary outcome measures showed a definite benefit of either treatment compared to the other in the long-term. More importantly, all outcome measures consistently showed a trend towards more events in patients allocated endovascular treatment. This is consistent with findings of SPACE and EVA-3S. These trials also found little difference in the rates of ipsilateral non-perioperative stroke more than 30 days after carotid stenting and endarterectomy over a shorter period of up to two and four years of follow-up, respectively (Eckstein *et al.* 2008; Mas *et al.* 2008), but both trials found an excess of events in stenting *versus* surgery in their overall analysis for time since randomisation.

Cranial nerve injury was significantly more frequent after surgery than after endovascular treatment. Not always are these benign and quickly resolving adverse events. One patient had only recovered from a cranial nerve injury by the 6-month follow-up. But it is very difficult to weigh cranial nerve injury against cerebrovascular events, which are much more likely to cause disability. Because of brain damage caused

by even a small procedural stroke, a patient may be less able to compensate for any future loss of function caused by subsequent strokes. Also, the fact that a particular patient has suffered a procedural stroke in the first place may point towards a lower tolerance of disturbances in blood supply and thus increasing the risk of future stroke. Stroke is also associated with an increased risk of dementia. Hospital-based series excluding pre-existing dementia reported a prevalence of post-stroke dementia at three months ranging from 6% (Madureira *et al.* 2001) to 28% (Pohjasvaara *et al.* 1997). A recent review reported a pooled prevalence of post-stroke dementia within three to six months of 18%, when pre-existing dementia was excluded (Pendlebury *et al.* 2009b). Cranial nerve palsies and stroke are therefore not readily comparable.

The exploratory subgroup analyses of patients treated with stenting compared to those treated with balloon angioplasty alone showed a higher risk of stroke that lasted for more than seven days or perioperative death in stented patients compared to those treated by balloon angioplasty alone, but the difference was not statistically significant (HR 1.37, 95% CI 0.74 to 2.52). The higher rate of events after stenting reflects the fact that in four out of 55 stented patients, stenting was performed as a secondary, rescue procedure after the onset of stroke caused by balloon dilation. Hence, this result does not reflect the current practice of carotid stenting as a primary procedure avoiding full balloon dilation. When perioperative events were excluded and thus the long-term efficacies of stenting and balloon angioplasty alone were compared, the risk of non-perioperative stroke or TIA was lower after stenting than after balloon angioplasty (HR 0.67, 95% CI 0.34 to 1.32) but this did not reach statistical significance.

CAVATAS was not sufficiently powered to show definite effects in any subgroup analysis. They were exploratory in nature and may inform future analysis carried out in much larger patient populations. None of the subgroup analyses of major risk factors conclusively favoured endovascular treatment over surgery. Endovascular treatment was somewhat safer in patients with less than 70% stenosis of the treated artery but the number of patients in this category was very small, resulting in a very wide confidence

interval. In patients with a history of ischaemic heart disease, the rate of stroke that lasted for more than seven days or perioperative death after carotid endarterectomy was lower than in patients without ischaemic heart disease, whereas after endovascular treatment the rate of this outcome measure was higher in the former patients compared to latter. The treatment-covariate interaction test approached statistical significance. This result may become significant with larger patient numbers or the apparent correlation could simply be due to chance since no correction for multiple comparisons was made.

The long-term risk of developing restenosis  $\geq 70\%$  was higher after endovascular treatment than after surgery with smoking independently predicting severe carotid restenosis during follow-up. Moreover, restenosis  $\geq 70\%$  was associated with an increased risk of ipsilateral cerebrovascular events during long-term follow-up.

Smoking is a recognised risk factor for stroke and guidelines uniformly advise smoking cessation as stroke preventive measure (Goldstein *et al.* 2006). Inflammatory mediators like CRP, interleukin-6 and white blood cells are raised in smokers. In turn, these inflammatory mediators are linked to atherosclerosis.

Smoking is also directly linked to endothelial dysfunction that can lead to atherosclerosis. However, the exact pathways of a causal relationship between smoking and cardiovascular risk factors is still unclear (Yanbaeva *et al.* 2007). The fact that smoking predicted severe carotid restenosis in both treatment groups is therefore plausible. To continue smoking after carotid surgery or endovascular treatment can be regarded counterproductive and patients should be strongly encouraged to stop smoking. Other mechanisms may also contribute to restenosis. Surgical and endovascular intervention only deal with the immediate consequences of atherosclerosis and not its underlying causes. It is therefore not surprising should the processes that led to the stenosis continue after plaque removal or stent insertion. In addition, the “damage” caused to the vessel wall by either plaque removal or balloon inflation and/or stent insertion may provide a stimulus for smooth muscle proliferation and intima-media thickening, which

in turn might lead to restenosis. This was shown to be the case in a patient with recurrent restenosis after angioplasty who underwent carotid endarterectomy, which showed prolific smooth muscle hypertrophy at the site of the previous angioplasty (Crawley *et al.* 1998). Accompanying long-term medical therapy has an important role to play in preventing restenosis.

The risk of restenosis  $\geq 70\%$  was lower after stenting than after balloon angioplasty alone but still higher than in case series of primary stenting, which have reported severe restenosis in 6% of patients after five years and moderate restenosis in up to 16% of patients (Lal *et al.* 2003; Wholey *et al.* 2003; Bergeron *et al.* 2005). Better ascertainment in the context of a clinical trial and differences in patient selection and criteria for grading restenosis may explain this difference. Stenting techniques also differed: Stenting in CAVATAS was primarily carried out after unsatisfactory balloon angioplasty. Only one other randomised clinical trial investigated the incidence of restenosis following stenting and carotid endarterectomy. After a relatively short follow-up of two years, the cumulative risk of severe restenosis or occlusion in that trial was reported as 10.7% after stenting and 4.6% after endarterectomy (Eckstein *et al.* 2008).

Severe carotid restenosis diagnosed within the first year following treatment was associated with an increased risk of subsequent ipsilateral cerebrovascular events. The risk of ipsilateral stroke in patients with  $\geq 70\%$  restenosis was not significantly increased from the risk in patients with  $< 70\%$  restenosis, albeit with wide confidence intervals due to the small number of patients reaching this endpoint. Nevertheless, the increased incidence of restenosis  $\geq 70\%$  in the endovascular group may explain the increase in non-perioperative ipsilateral stroke and TIA after endovascular treatment.

A history of smoking independently predicted restenosis in CAVATAS and has been previously identified as predictor of restenosis after endarterectomy (Lattimer *et al.* 1997). The lack of interaction between treatment received and smoking in the prediction of restenosis suggests that the effect of smoking is similar in both treatment arms.

More than half of the recurrent cerebrovascular events in patients with severe restenosis were transient in nature. Any decision to re-treat patients with severe asymptomatic carotid stenosis based on ultrasound findings needs to take into account the relatively low risk of ipsilateral stroke in these patients, which was about 2% per year in CAVATAS.

No broadly accepted ultrasound criteria exist for the diagnosis of *de novo* restenosis. The same criteria used for calculating stenosis were used for establishing restenosis in CAVATAS, which may have led to an overestimate of restenosis in stented patients due to reduced vessel wall compliance (Nederkoorn *et al.* 2009).

Overall, the results of CAVATAS do not support a change in clinical practice away from carotid endarterectomy as treatment of choice but they support the use of endovascular treatment to prevent long-term stroke in patients in whom carotid endarterectomy is contraindicated or who prefer to undergo the possibly greater hazard of endovascular treatment in preference to surgery. Because none of the performed analyses favoured endovascular treatment over surgery and uncertainty regarding the long-term durability of endovascular treatment persists, it would be unjustified to recommend endovascular treatment as first-line treatment. It remains to be seen if changes in technology improve the safety of endovascular treatment. However, both EVA-3S with a definite benefit of surgery and SPACE with an inconclusive result cast some doubt on this assumption and the results of ICSS should provide more insight.

The results emphasise the need for further data from short and long-term comparisons of endovascular treatment with endarterectomy to clarify if the small differences between the treatments become significant with larger numbers of patients. While restenosis was more frequent following endovascular treatment further data are needed to confirm if stenting is superior to balloon angioplasty alone and comparable to surgery in preventing restenosis and if re-treatment of asymptomatic restenosis is justified.

### 9.3 Endovascular Treatment in Patients Not Suitable for Surgery – Comparison with Medical Care

Treating symptomatic carotid stenosis poses a dilemma in patients who are not well enough to undergo surgery or in whom surgery is thought to carry too high a risk of complications. Before endovascular treatment was available, patients not fit for surgery were treated medically. The advent of endovascular treatment with balloon angioplasty and stenting was a welcome addition to the management of these patients and quickly gained widespread acceptance. Endovascular treatment was thought to be suitable for patients not well enough for surgery and superior to medical treatment alone in preventing stroke recurrence. But there is little evidence from randomised controlled trials of the safety and long-term effectiveness of this treatment.

CAVATAS therefore contained a randomised trial comparing the long-term outcome of endovascular treatment of carotid stenosis compared to medical therapy alone. This study was called CAVATAS-MED.

#### 9.3.1 Methods and Patients

##### Patients

Patients with carotid stenosis who were considered not suitable for carotid endarterectomy were randomly allocated to receive either endovascular treatment or medical therapy alone. Twelve centres enrolled patients into CAVATAS-MED. These centres are listed in the Appendix.

Other inclusion criteria and a detailed description of baseline investigations, randomisation, definition of outcome, treatment, and follow-up are set out above and will not be repeated here. Arrangements for follow-up differed in so far as patients randomised to medical therapy alone had the initial follow-up appointment one month after randomisation.



## **Outcome Measures**

Stroke or death during follow-up was chosen as primary outcome measure. Since the study sample was very small, only one further outcome measure was analysed and included all cerebrovascular events (Amaurosis fugax, retinal infarct, TIA and stroke).

## **Statistical Analysis**

Data were analysed based on intention to treat using standard statistical software (SPSS for Macintosh, SPSS Inc., Chicago, Illinois, USA). The log rank test was used to compare the survival free experience in the two treatment arms. The treatment effect was estimated using a Cox proportional hazard model to calculate hazard ratio and 95% confidence intervals. The medical therapy group was used as the reference group. The proportional hazards assumption was tested with a graphical log-minus-log method. All outcome events up to the last available follow-up or death of the patient were included in the calculation of hazard ratios. To be consistent with the CAVATAS data presentation, Kaplan-Meier curves were only plotted up to eight years of follow-up.

### **9.3.2 Results**

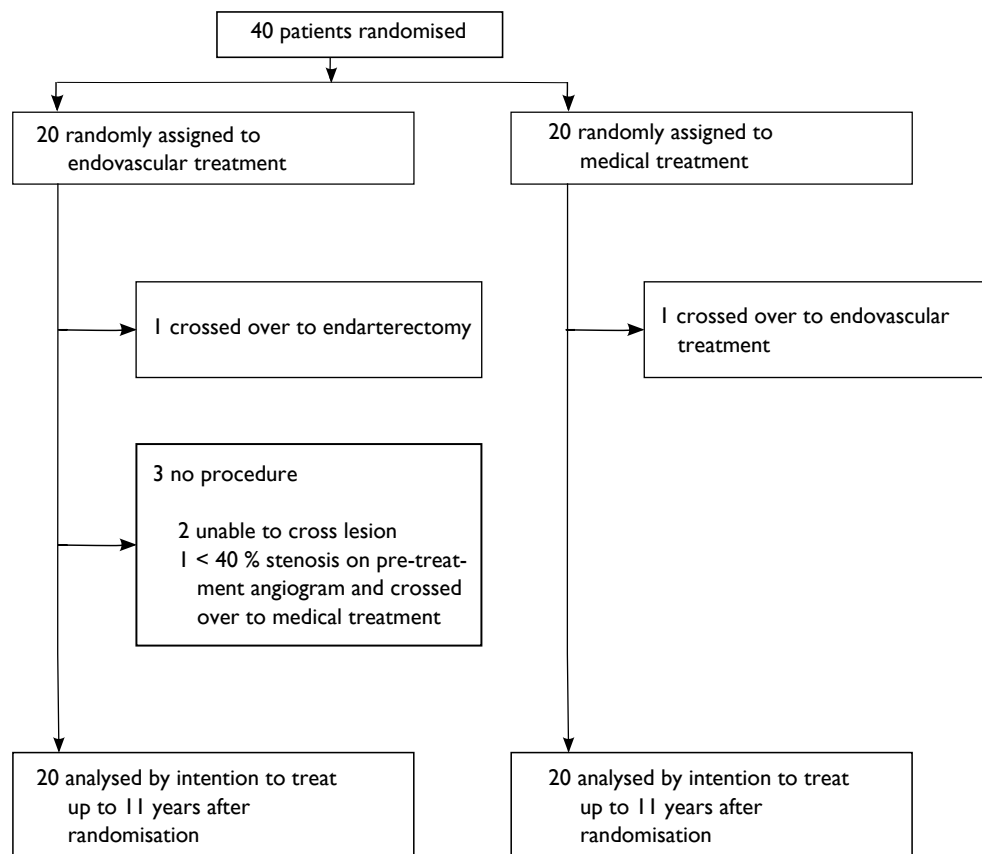
#### **Baseline Characteristics**

The first patient not suitable for surgery was randomised on 29 April 1992. By the time the last patient was randomised on 16 May 1997, a total of 40 patients not suitable for surgery were randomly assigned to endovascular treatment (n = 20 patients) or medical therapy alone (n = 20 patients).

In 31 patients the reasons for being considered unsuitable for carotid endarterectomy were either surgical (n = 17) or medical (n = 14) contraindications. Seven patients fulfilling the inclusion criteria for the main CAVATAS study had refused surgery and were therefore included in this study and in two patients no reason for being unsuitable for surgery was recorded.

Four patients in the endovascular group did not undergo their allocated treatment: Two patients crossed over to medical therapy after it proved impossible to cross the lesion with the guide wire. One patient refused endovascular treatment after randomisation and had carotid endarterectomy instead. One patient was randomised based on an angiogram prior to study entry suggesting greater than 50% stenosis. At the time of endovascular treatment the angiogram did not confirm this but showed a stenosis < 40% and treatment was not carried out. One patient in the medical therapy group underwent endovascular treatment at the patient's request but the treatment failed to dilate the stenosis (Figure 9.34).

Figure 9.34 – CAVATAS-MED: Trial profile



The majority of patients (62.5%) had experienced cerebrovascular symptoms in the six months leading up to randomisation (Table 9.8). Patients allocated to endovascular

treatment were younger than the patients assigned to medical therapy and more patients in the latter group had a history of ischaemic heart disease or previous myocardial infarction. Cholesterol was elevated in more patients in the endovascular treatment group. Other baseline patient characteristics did not differ between the two groups (Table 9.9 and Figure 9.35).

Blood pressure control during the course of the trial was similar in both treatment groups (Figure 9.36) as was the number of patients receiving anti-platelet therapy.

Data on the use of cholesterol-lowering and anti-hypertensive medication was not collected.

**Table 9.8 – CAVATAS-MED: Cerebrovascular symptoms prior to randomisation per allocated treatment**

*Data are number of patients (% of known data), unless otherwise indicated. EVT, endovascular treatment; MED, medical treatment.*

|                            | EVT<br>(n = 20) | MED<br>(n = 20) |
|----------------------------|-----------------|-----------------|
| Transient ischaemic attack | 6 (30%)         | 3 (15%)         |
| Amaurosis fugax            | 0               | 3 (15%)         |
| Hemisphere stroke          |                 |                 |
| Minor                      | 2 (10%)         | 0               |
| Major, non-disabling       | 4 (20%)         | 0               |
| Major, disabling           | 1 (5%)          | 1 (5%)          |
| Asymptomatic               | 5 (25%)         | 10 (50%)        |
| Unknown                    | 2 (10%)         | 3 (15%)         |

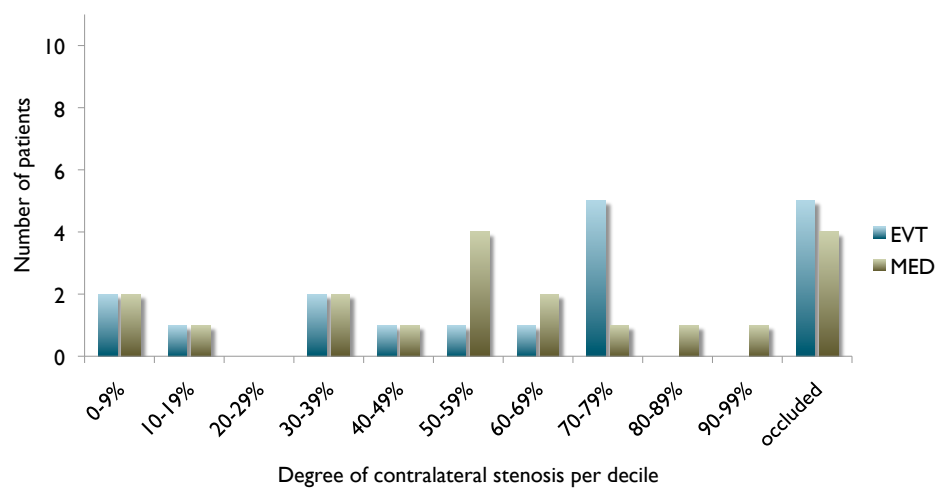
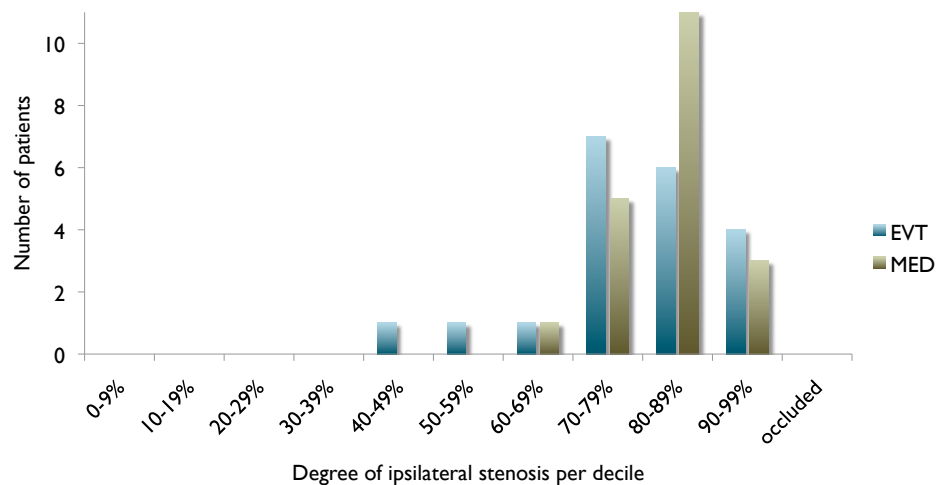
**Table 9.9 – CAVATAS-MED: Patient characteristics at baseline per allocated treatment**

Data are number of patients (% of known data), unless otherwise indicated. EVT, endovascular treatment; MED, medical treatment; SD, standard deviation; IQR, interquartile range.

|  | <b>EVT<br/>(n = 20)</b> | <b>MED<br/>(n = 20)</b> |
|--|-------------------------|-------------------------|
| <b>Age (median [IQR], years)</b>                                 | 67 [59 – 72]            | 71.5 [69 – 79]          |
| <b>Sex</b>   |                         |                         |
| Women  | 16 (80%)                | 15 (75%)                |
| Men  | 4 (20%)                 | 5 (25%)                 |
| <b>Vascular risk factors</b>                                     |                         |                         |
| Hypertension   | 14 (70%)                | 13 (65%)                |
| Systolic blood pressure (mean [SD], mmHg)                        | 147 [21]                | 151 [21]                |
| Diastolic blood pressure (mean [SD], mmHg)                       | 83 [6]                  | 82 [9]                  |
| Diabetes mellitus  | 6 (30%)                 | 6 (30%)                 |
| Cholesterol > 6.5 mmol/L   | 13 (65%)                | 3 (15%)                 |
| Smokers, past or present   | 17 (85%)                | 13 (65%)                |
| <b>Prior history of cardiovascular disease</b>                   |                         |                         |
| Myocardial infarction  | 1 (5%)                  | 4 (20%)                 |
| Ischaemic heart disease  | 5 (25%)                 | 8 (40%)                 |
| Atrial fibrillation  | 0                       | 0                       |
| Peripheral vascular disease                                      | 4 (20%)                 | 3 (15%)                 |
| <b>Treatments used at randomisation</b>                          |                         |                         |
| Antiplatelet   | 19 (95%)                | 20 (100%)               |
| Warfarin   | 2 (10%)                 | 1 (5%)                  |
| <b>Time from randomisation to treatment (median [IQR], days)</b> | 39 [23 – 72]            | –                       |

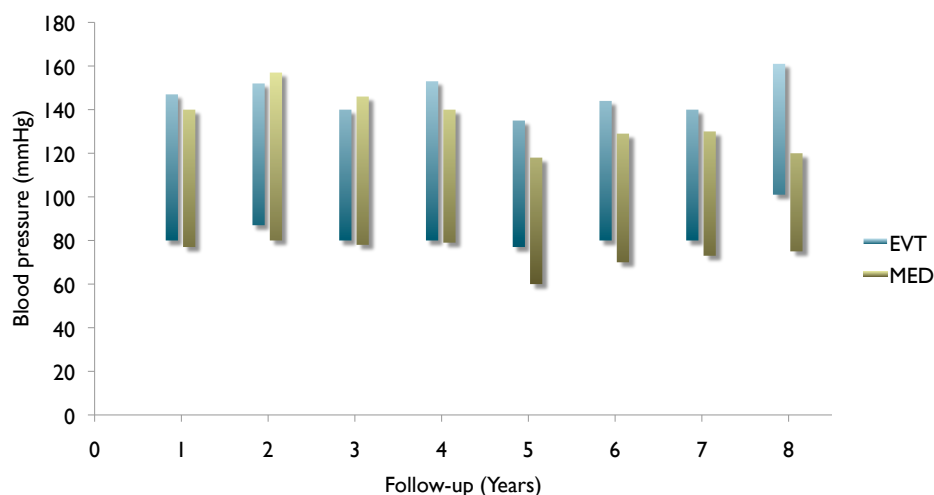
**Figure 9.35 – CAVATAS-MED: Baseline degree of stenosis per allocated treatment**

Shown is the degree of stenosis (% per decile) in the randomised ipsilateral internal carotid artery (upper graph) and the contralateral internal carotid artery (lower graph). EVT, endovascular treatment; MED, medical treatment.



**Figure 9.36 – CAVATAS-MED: Blood pressure during follow-up per allocated treatment**

Shown is the mean blood pressure at randomisation (mmHg). The bottom of each bar indicates the diastolic BP, the top of each bar represents the systolic blood pressure



### Delay to Treatment

The median delay between randomisation and first endovascular treatment was 27 days (IQR 8 to 49 days). One patient suffered a retinal infarct while awaiting endovascular treatment.

### Follow-up

Patients were followed up for up to ten years. The median length of follow-up was 4.5 years (IQR 1.25 to 7 years) in the endovascular treatment group and 3.5 years (IQR 1 to 8 years) in the medical treatment group.

### Primary Outcome

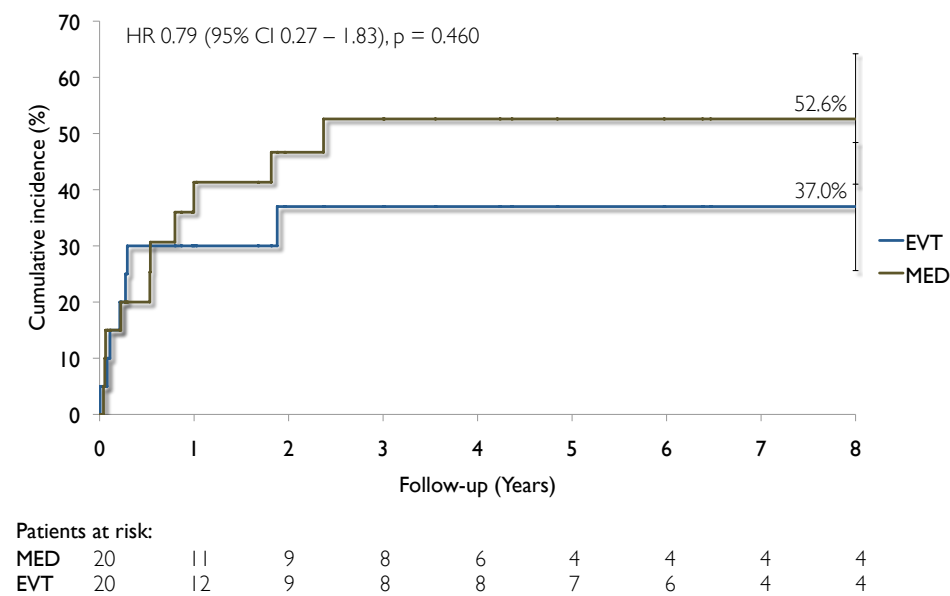
Stroke or death occurred in nine patients in each treatment group. Stroke contributed five events in the endovascular treatment group and four events in the medical therapy group to this outcome cluster. One fatal haemorrhagic stroke occurred one day after endovascular treatment in addition to a retinal infarct that occurred between randomisation and angioplasty.

The 3-year cumulative incidence of stroke or death was 36.0% (SE 10.9%) after endovascular treatment and 35.4% (SE 10.8%) after medical therapy. Eight years after randomisation, the cumulative incidence of stroke or death was 52.0% (SE 13.0%) in the former and 41.3% (SE 11.3%) in the latter treatment group (Figure 9.37).

The hazard ratio based on all available follow-up data showed no difference between endovascular treatment and medical therapy (HR 1.02, 95% CI 0.41 to 2.57, Figure 9.38).

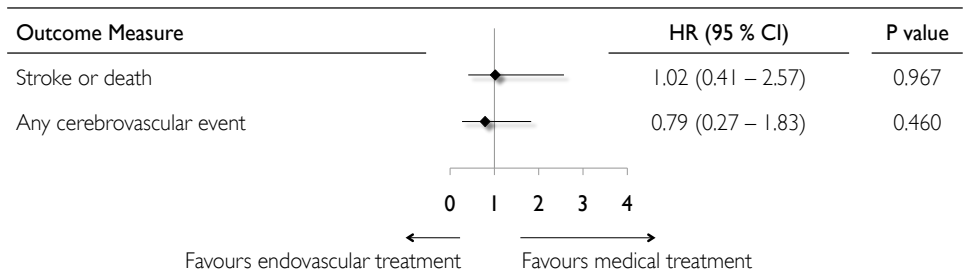
**Figure 9.37 – CAVATAS-MED: 8-year cumulative incidence of stroke or death**

Shown is the Kaplan-Meier cumulative incidence of stroke or death during 8 years of follow-up. The vertical bars at the end of each line represent the standard errors of the 8-year cumulative incidence. EVT, endovascular treatment; MED, medical treatment.



**Figure 9.38 – CAVATAS-MED: Hazard ratios for outcome measures (ITT)**

HR, hazard ratio; CI, confidence interval.



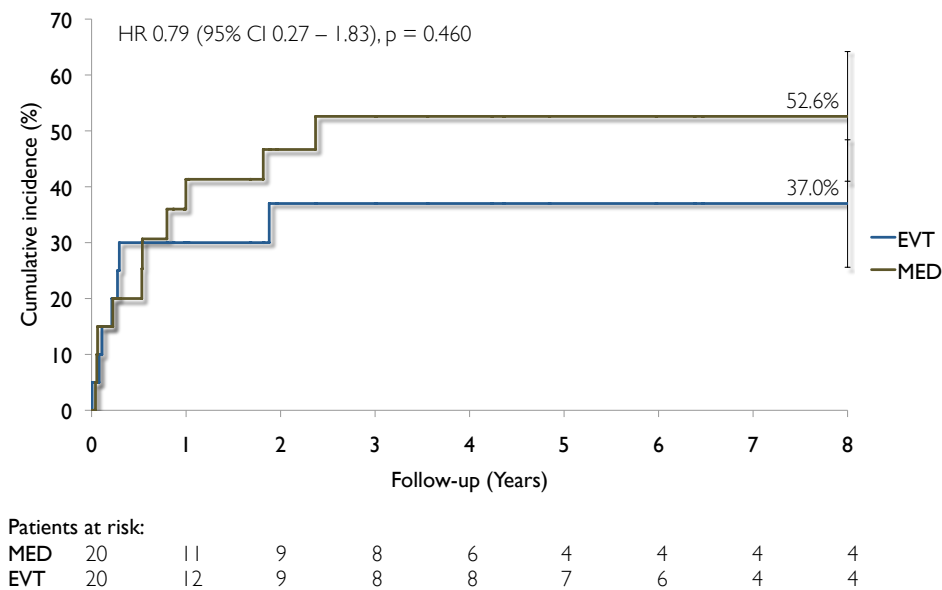
Secondary Outcome Measure

The combined outcome of TIA, stroke, amaurosis fugax, and retinal infarct occurred in seven patients in the endovascular treatment group and in ten patients in the medical therapy group.

The 8-year cumulative incidence of any cerebrovascular event was 37.0% (SE 11.4%) after endovascular treatment and 52.6% (SE 11.6%) with medical therapy alone (Figure 9.39). All events occurred within three years after randomisation. The reduction in risk after endovascular treatment was not statistically significant (HR 0.79, 95% CI 0.27 to 1.83, Figure 9.38).

Figure 9.39 – CAVATAS-MED: 8-year cumulative incidence of any cerebrovascular event (ITT)

Shown is the Kaplan-Meier cumulative incidence of any cerebrovascular event (amaurosis fugax, retinal infarct, transient ischaemic attack, or stroke) during 8 years of follow-up. The bars at the end of each line represent the standard errors of the 8-year cumulative incidence.





### 9.3.3 Discussion

Endovascular treatment by balloon angioplasty or stenting was associated with a 5% (95% CI 0.1 to 24.9%) risk of stroke or death within 30 days after treatment. Thereafter, the risk of stroke was 10% (95% CI 0.1 to 43.7%) in patients allocated endovascular treatment. However, the rate of stroke with medical therapy alone over the whole study was only 20% (95% CI 0.1 to 31.6%) and the number of events prevented by endovascular treatment did not make up for the initial risk of the procedure. CAVATAS-MED therefore failed to conclusively show superiority of endovascular treatment over medical therapy for carotid stenosis in patients not suitable for carotid endarterectomy.

Because CAVATAS-MED had a very small sample size it would be wrong to form any firm conclusions about the lack of benefit of endovascular treatment. The wide confidence intervals and large standard errors surrounding the calculated risks and hazard ratios show that the study was underpowered to show any effect of treatment. It remains possible that endovascular treatment could be superior or indeed worse than medical therapy alone in the kind of patients randomised to CAVATAS-MED.

The small sample size reflects the fact that there are few patients with carotid stenosis who are not suitable for surgery but still appropriate for endovascular treatment. Over 500 patients were randomised between carotid endarterectomy and endovascular treatment but only 40 patients were considered unsuitable for surgery at the same centres (of which 7 were included on the grounds of having refused surgery and 1 underwent surgery despite having been considered unsuitable). This may reflect the practice that was common during randomisation in CAVATAS of only investigating patients for carotid stenosis and referring them to the CAVATAS centres if they were initially considered suitable for surgery. Moreover, reasons for considering patients unsuitable for surgery are very poorly defined and with carotid endarterectomy increasingly being carried out under local anaesthesia few contraindications for surgery other than anatomical reasons (stenosis too high to be accessible by surgery) exist.

Patients assigned to endovascular treatment were considerably younger and more patients in this treatment group had elevated cholesterol levels at time of randomisation compared to those allocated medical therapy alone. It could have been anticipated that the age profile would favour endovascular treatment but this is not reflected by the trial results. Modern medical therapy might have reduced the rate of stroke and rendered endovascular treatment even less effective.

The trial protocol did not specify targets for blood pressure control or cholesterol levels. Antiplatelet therapy was widely implemented but no data relating to the use of lipid-lowering or anti-hypertensive medication during follow-up were collected. This makes it difficult to assess the quality of medical therapy in the trial and compare it to modern treatment regimes.

The median delay between randomisation and endovascular treatment was longer than in the CAVATAS study described in the beginning of this chapter and one patient suffered a retinal infarct while awaiting endovascular treatment. This may be a result of more investigations being carried out to establish the suitability for surgery in more severely ill patients and thus delaying treatment.

Interventionists may take some encouragement from the fact that of the seven patients treated with stenting only one had a non-disabling stroke during follow-up, while eight primary outcome events were recorded in the remaining patients in the endovascular treatment group. Stenting technology has evolved since CAVATAS was conducted, although the rate of stroke within 30 days after carotid stenting was still higher than that after carotid endarterectomy in the recent trials (Mas *et al.* 2006; Ringleb *et al.* 2006).

Only one other randomised trial has compared endovascular treatment to medical therapy for carotid stenosis in patients not suitable for carotid endarterectomy and was similarly hampered by a very small sample size. This study randomised 21 patients with bilateral carotid stenosis between stenting and medical care (Zhao *et al.* 2003). After 18 months of follow-up, one in eight patients had suffered a stroke or had died after stenting

(12.5%) compared to nine in 13 medically treated patients (69.2%). The higher rate of stroke or death in the Chinese study may reflect the fact that these patients had severe bilateral carotid stenosis. Alternatively, differences in risk factor profile or the quality of medical therapy may account for the difference in risk of stroke or death between the Chinese study and CAVATAS-MED.

CAVATAS-MED represents the largest randomised body of data comparing endovascular treatment to medical therapy alone although it failed to recruit sufficient numbers of patients to show any effect of interventional treatment with a sufficient level of certainty. Medical therapy has evolved since the trial was conducted. Especially the use of cholesterol-lowering statins and better control of hypertension have undoubtedly improved medical therapy. It remains uncertain what the best management of patients not suitable to undergo carotid endarterectomy should be and more information on how interventional treatment, be it surgical or endovascular, compares to modern medical therapy would be desirable. It could even be argued that another trial in symptomatic patients that includes modern medical therapy as a separate arm with a pre-defined medical regimen to be followed by participants is needed. The cholesterol and blood pressure trials have shown that the preventive effect of the tested medication went beyond mere blood pressure and cholesterol lowering and it would therefore be difficult to define the medical regimen by its control of target parameters. With the positive publicity of carotid endarterectomy it is also unclear how such a trial would be accepted by patients and clinicians, potentially making recruitment very difficult. One such trial is underway in asymptomatic patients (Reiff *et al.* 2009).

## 10 Putting CAVATAS in the Context of Other Trials – A Cochrane Systematic Review

### 10.1 Introduction

The first Cochrane Review comparing endovascular treatment and endarterectomy for carotid artery stenosis was carried out in 1997. At that time data on the safety and efficacy of endovascular treatment was scarce and the review did not identify any completed randomised trials (Crawley *et al.* 2000). The only sources of data were non-randomised case series, registries or case reports (Wiggli *et al.* 1983; Tsai *et al.* 1986; Theron *et al.* 1987; Brown *et al.* 1990; Theron *et al.* 1990; Kachel *et al.* 1991; Munari *et al.* 1992; Eckert *et al.* 1996; Gil-Peralta *et al.* 1996; Theron *et al.* 1996).

CAVATAS was one of the earliest randomised clinical trials of endovascular treatment of carotid stenosis and the first to indicate that endovascular treatment may be comparable to endarterectomy with regards to safety and efficacy in preventing stroke. By the time the early results of CAVATAS were published in 2001, primary stenting had largely replaced balloon angioplasty alone. The rationale for this change in technique was that stenting might avoid the consequences of carotid dissection caused by balloon dilation by maintaining laminar flow across the stenosis and sealing the site of dissection and thus preventing a free intimal flap from which thromboembolism might originate (Diethrich *et al.* 1996; Roubin *et al.* 2001). The hope was that results from intervention in the coronary artery circulation, where stenting had been shown to be superior to balloon angioplasty alone could be mirrored in the carotid artery (Fischman *et al.* 1994; Serruys *et al.* 1994).

The changes in technology of endovascular treatment and remaining uncertainty about safety and efficacy of endovascular treatment highlighted by the initial Cochrane review led to other trials being conducted in the years following CAVATAS. Neither of them provided sufficient evidence on their own that would have settled the debate as to the

ideal treatment of patients with symptomatic stenosis. Combining results from similar trials in a meta-analysis is one way of trying to increase the certainty about available evidence and different attempts at such combined analyses have been made.

Before discussing the Cochrane Review on endovascular treatment of carotid stenosis carried out in 2007 in particular, it is useful to provide a brief overview of what sets Cochrane Reviews apart from other reviews.

## **10.2 Cochrane Review Explained**

Healthcare research provides unmanageable amounts of information. Cochrane reviews aim at bringing together all available evidence for and against the appropriateness of particular treatments or interventions in the absence of definitive randomised trials. These reviews are published quarterly in the Cochrane Library by the Cochrane Collaboration and provide up-to-date information for healthcare professionals and are influential in shaping policies for healthcare provision. Information gained from such reviews help to formulate research questions for trials and determine the sample size needed to answer any question posed by the review in the absence of definitive clinical trials. Most funding bodies require researchers to carry out a Cochrane-style review prior to applying for funding.

A systematic review is focused on a specific research question. Evidence from research is collated, analysed, and interpreted based on pre-defined inclusion criteria. Bias is minimized by using systematic methods in order to provide reliable findings and conclusions.

Cochrane reviews are characterised by clearly stated objectives and pre-defined inclusion criteria and a reproducible methodology. A comprehensive search strategy is aimed at identifying all studies meeting the inclusion criteria published in the international literature. The identified studies are assessed for the validity of their findings and characteristics and findings of included studies are presented in a systematic fashion.

Cochrane reviews often contain meta-analyses using statistical methods to summarize the results of independent studies (Glass 1976). Two different methods (fixed effect and random effects method) were used for the meta-analysis for dichotomous outcomes in the review discussed below. In meta-analyses that bring together studies of small sample size or with low event rate, the Mantel-Haenszel method has better statistical properties than the inverse variance method sometimes used for meta-analyses and was the method chosen for the review.

The random effects method assumes that different studies are estimating different, yet related intervention effects. When heterogeneity is absent, the fixed effect and random effects methods will give identical results. With heterogeneity present, the confidence intervals will be wider in the random effects model and corresponding claims of statistical significance therefore more conservative.

This systematic and comprehensive approach sets Cochrane reviews apart from other reviews that are very often limited to publications in English identified by a cursory search on Medline and restricted by a mere meta-analysis of the main findings without a detailed assessment of the individual trials' quality.

### **10.3 The Evidence for Endovascular Treatment vs. Surgery for Carotid Stenosis**

#### **10.3.1 Objective of Review**

The purpose of this Cochrane review was to bring together the published evidence from clinical trials comparing endovascular treatment of internal carotid artery stenosis compared to surgery or medical treatment in the absence of definitive clinical trials. The main work was published in the Cochrane Library (Ederle *et al.* 2007a) and presented at the Autumn Meeting of the Association of British Neurologists (Ederle *et al.* 2008b). Aspects of the work have been published elsewhere (Ederle *et al.* 2009c). Since the Cochrane review was conducted, one further trial that was listed in the Cochrane review as 'ongoing' has published 30-day safety results. This trial will be discussed in detail in the next section and is not included in this chapter's review.

### 10.3.2 Outcome Measures

It was planned to analyse outcomes with intention to treat. In order to compare safety and efficacy of endovascular treatment to surgery or medical treatment alone, two main hypotheses were investigated:

- Whether endovascular treatment for carotid artery stenosis has a significantly different risk of periprocedural stroke or death compared to surgery or medical treatment
- Whether endovascular treatment for carotid artery stenosis is effective in preventing stroke ipsilateral to the procedure and in other territories in the long term

Secondary analyses were carried out to examine whether

- Endovascular treatment reduces the risk of cranial neuropathy
- Treatments differed in terms of any death within 30 days of procedure, any stroke within 30 days of procedure and any death of any cause following treatment
- The rates of other vascular complications (myocardial infarction, pulmonary embolism, haematoma) differ between endovascular treatment and surgery
- There is a significant difference in the restenosis rates following endovascular treatment or carotid endarterectomy and whether restenosis leads to recurrent stroke
- In patients unsuitable for surgery, carotid angioplasty and stenting are more effective in preventing stroke compared to medical therapy
- There is a learning curve, i.e. whether the event rate changes over time within trials and from trial to trial

- The endovascular treatment or carotid endarterectomy arm is responsible for heterogeneity among the trials
- Stenting with cerebral protection devices has a lower rate of treatment-related ischaemic events than stenting without cerebral protection devices
- Endovascular treatment is as safe as surgery in asymptomatic patients.

### 10.3.3 Selection of Studies

Un-confounded truly randomised trials comparing carotid angioplasty or stenting (or both) with conventional carotid endarterectomy or medical therapy alone were included in the review. Trials including patients of any age or sex with either symptomatic or asymptomatic carotid stenosis were considered. Any acceptable technique for carotid endarterectomy and any acceptable endovascular technique for treatment of carotid stenosis were allowed and trials of patients with bilateral as well as unilateral procedures were reviewed.

The Cochrane Stroke Group trials register was searched in March 2007 in addition to the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 1, 2007), MEDLINE (1950 to March 2007), EMBASE (1980 to March 2007), and Science Citation Index (1945 to March 2007). The detailed search strategy for MEDLINE (Ovid) was adopted for the other databases and can be found in the Appendix. In an effort to identify further published, unpublished and ongoing trials, reference lists of relevant articles were reviewed and individuals active in the field were contacted.

All articles identified by the different database searches were reviewed for their suitability to be included in the review and pre-specified data were extracted:

- The method of randomisation and whether the randomising doctor was blinded to the treatment allocated
- The number of patients originally allocated to each treatment group. This was done to enable an intention-to-treat analysis



- The method of measuring outcome and whether outcome assessment was independent or blinded or both
- The number of exclusions and losses to follow up
- Intervention characteristics
- Outcome measures as outlined above

A number of subgroup analyses were identified prior to data collection and relevant information was also extracted from the published articles:

- The number of patients given antiplatelet or anticoagulant drugs within the treatment period
- The proportion of symptomatic versus asymptomatic patients in each treatment group
- The degree of baseline stenosis in each treatment group
- Stents versus no stents
- The use of cerebral filter devices versus no cerebral filter device.

Heterogeneity among trials was tested using a standard  $\chi^2$  test and  $P = 0.1$  was chosen as level of statistical significance as far as heterogeneity tests were concerned. The odds of an unfavourable outcome in patients treated by endovascular intervention compared to the corresponding odds in patients treated medically or surgically (odds ratio) with corresponding 95% confidence interval were calculated using the Mantel-Haenszel fixed effect method. In light of anticipated heterogeneity among trials, the odds ratio was also calculated using the Mantel-Haenszel random effects model.  $P = 0.05$  was chosen as level of statistical significance.

#### 10.3.4 Description of Studies

The characteristics of the studies included in this review are summarised in Table 10.1.

##### Included Studies

Seven completed randomised trials were identified comparing endovascular treatment with surgery or medical care, involving 941 patients (Brooks *et al.* 2001; Brown *et al.* 2001; Brooks *et al.* 2004; Hoffmann *et al.* 2006; Ederle *et al.* 2007b).

The majority of patients (n = 2,286) were however contributed from five further randomised trials that had been stopped early (Naylor *et al.* 1998; Alberts 2001; Yadav *et al.* 2004; Mas *et al.* 2006; Ringleb *et al.* 2006).

##### Completed Trials

The multi-centre trial CAVATAS was described in detail in the previous section. The initial analysis of the 505 patients allocated to either endovascular treatment or surgery was presented in 2001 and the analysis of the 40 patients unsuitable for surgery and randomised between endovascular and medical treatment was first presented at the European Stroke Conference in 2007 (Ederle *et al.* 2007b).

A group that had collaborated in CAVATAS continued randomisation after CAVATAS and presented the local results of 20 patients randomised between carotid endarterectomy and endovascular treatment in 2006 (Hoffmann *et al.* 2006). This trial will be called BACASS in this review.

A single centre study carried out in Kentucky, USA compared carotid endarterectomy with carotid angioplasty and stenting in 104 symptomatic patients and published in 2001 (Brooks *et al.* 2001). The same group subsequently published a similar study in 85 asymptomatic patients (Brooks *et al.* 2004).

Two trials were identified that had been carried out in China. The multicentre trial of endarterectomy versus stenting for treatment of carotid atherosclerotic stenosis in China (TESCAS-C) reported the results of 166 patients randomised between carotid stenting

and surgery for symptomatic carotid stenosis (Ling *et al.* 2006). The other single centre trial compared endovascular treatment and medical care in 21 patients with bilateral carotid stenosis and was carried out in Beijing (Zhao *et al.* 2003).

#### Stopped Trials

A trial of endovascular treatment versus surgery was started at Leicester Royal Infirmary, UK, around the same time as CAVATAS but was suspended after only 23 patients had been randomly allocated to treatment and only 17 patients had proceeded to treatment. No complications occurred in the ten carotid endarterectomies but five of the seven patients undergoing endovascular treatment suffered a stroke. Three patients were excluded from the trial after randomisation: One patient due for surgery asymptotically occluded the carotid artery before treatment could be carried out and one patient in each group refused treatment. The remaining three patients were awaiting hospital admission at the time the trial was stopped.

A multicentre trial of carotid stenting versus endarterectomy (Wallstent) in the USA was also suspended early after enrolling 219 patients. Reportedly, this was because of a significant lower complication rate in the stenting group compared to endarterectomy (4.5% versus 21.1%,  $P = 0.049$ ), but no results were ever published in a peer-reviewed journal (Alberts 2001).

The randomised Stenting and angioplasty with protection in patients at high risk for endarterectomy (SAPPHIRE) trial of stenting using a single device (Angioguard XP emboli protection guide wire) compared to endarterectomy in 334 high surgical risk was stopped after a drop in recruitment numbers (Yadav *et al.* 2004).

Similar reasons led to the early termination of the Stent-Protected Angioplasty versus Carotid Endarterectomy study (SPACE) in symptomatic patients. Interim-analysis of the 1,183 patients randomised at the time revealed that almost twice as many patients were required for a statistically significant result and the investigators decided to stop randomisation (Ringleb *et al.* 2006).

The Endarterectomy Versus Angioplasty in patients with Symptomatic Severe carotid Stenosis (EVA-3S) was a multicentre trial in France and randomised 527 patients before it was stopped due to safety and futility concerns. The 30-day risk of stroke or death was significantly higher after stenting than after surgery (9.6% versus 3.9%) and the Safety Committee recommended stopping the trial (Mas *et al.* 2006).

#### Ongoing Trials

Several trials comparing endovascular treatment to carotid endarterectomy or medical therapy were ongoing at the time of this review:

A trial comparing stenting and carotid endarterectomy within one month of TIA or stroke was initiated in 2005 (Agostoni *et al.* 2005).

The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST, NCT00004732) is comparing endovascular treatment and carotid endarterectomy in symptomatic and asymptomatic patients and was still recruiting patients in the United States of America and Canada at the time of this review (Hobson 2002).

A study in Germany with the aim of recruiting 200 patients with symptomatic carotid stenosis and comparing carotid stenting and endarterectomy was under way (Link *et al.* 2000).

A commercially sponsored multi-centre trial called 'Carotid Angioplasty and Stenting Versus Endarterectomy in Asymptomatic Subjects Who Are at Standard Risk for Carotid Endarterectomy With Significant Extracranial Carotid Stenotic Disease' (ACT I, NCT00106938) is enrolling patients in the USA.

The Asymptomatic Carotid Surgery Trial-2 (ACST-2, ISRCTN 21144362) was about to start enrolment.

The International Carotid Stenting Study (ICSS) was still ongoing but has since completed randomisation. It will be discussed in the following chapter.

## Methodological Quality of Included Studies

### Centre and patient requirements

CAVATAS was a multicentre trial with long-term follow-up beyond five years. Each centre had to have a team consisting of a neurologist or physician interested in stroke medicine for follow-up, an experienced vascular surgeon to perform the endarterectomies and either a vascular radiologist with angioplasty experience or interventional neuroradiologist to perform carotid angioplasty and stenting. In CAVATAS, patients with symptomatic or asymptomatic carotid stenosis with any degree of stenosis equally suitable for surgery or endovascular treatment were eligible provided the clinician was substantially uncertain about the best treatment. No specific technique was prescribed for surgical treatment and all endovascular techniques were allowed.

Patients unsuitable for surgery were randomised in CAVATAS-MED between endovascular treatment and medical therapy.

BACASS recruited patients with symptomatic carotid stenosis greater than 70% and suitable for both surgery and endovascular treatment. Patients had to be willing and available to be followed up for two years and each case was discussed in a multi-disciplinary meeting prior to randomisation.

The Kentucky study was a single centre trial and only included symptomatic patients with symptoms or signs of cerebra ischaemia confined to the ipsilateral carotid artery within three months prior to randomisation. The degree of stenosis had to be greater than 70%.

The same group carried out a single centre study in patients who did not have signs or symptoms of cerebral ischaemia and a degree of carotid stenosis of at least 80%, documented by digital subtraction angiography.

TESCAS-C enrolled patients with severe symptomatic or asymptomatic carotid stenosis. No further details regarding exact degree of stenosis, centre requirements and further inclusion criteria were available from the abstract of the Chinese publication.

Patients with severe carotid stenosis on one side and contralateral occlusion as demonstrated on duplex ultrasound or cerebral angiography were eligible to join the single centre study carried out in Beijing, China. This study did not publish further centre requirements or inclusion criteria.

The study carried out in Leicester, UK recruited patients with symptomatic severe internal carotid artery stenosis greater than 70%. Endarterectomy was carried out by standardised operative technique by a single consultant vascular surgeon. Endovascular treatment was carried out by a single consultant vascular radiologist using stents in all patients.

Patients with symptomatic carotid artery stenosis greater than 60% with transient ischaemic attacks or completed strokes within 120 days prior to randomisation were randomised in the Wallstent study. Each participating centre had to demonstrate that it had the personnel, technical experience and infrastructure to support the study. This included an interventionist, surgeon, neurologist, ultrasonographer and study co-ordinator. The study was only presented at a conference and no further details regarding centre or patient requirements were available from the abstract. Controversially, the study sponsor directly intervened in the conduct of the trial and terminated the trial prematurely.

SAPPHIRE randomised symptomatic and asymptomatic patients who were perceived to have a high surgical risk to either protected stenting or endarterectomy. The degree of carotid stenosis had to be greater than 50% in symptomatic patients and greater than 80% in asymptomatic patients. In addition, high surgical risk was determined by the presence of at least one of the following co-morbidity conditions: congestive heart failure, left ventricular dysfunction, recent myocardial infarction or severe pulmonary disease. A

consensus decision to offer inclusion in the study was reached by a neurologist, surgeon and interventionist.

The multi-centre EVA-3S study recruited patients with recently (within 120 days prior to randomisation) symptomatic carotid stenosis greater than 60%. Patients were only included in the trial if they had made a useful recovery from their stroke (modified Rankin Score less than 3). Participating surgeons were required to have the experience of at least 25 carotid endarterectomies in the year before joining the trial. The interventionist had to have performed at least 12 carotid stenting procedures or at least 25 stenting procedures of the supra-aortic trunks including five carotid stents. Less-experienced operators and interventionists were allowed to join but procedures had to be carried out under supervision. The trial briefly interrupted randomisation and the use of cerebrovascular filter devices were made compulsory in the endovascular treatment arm.

SPACE recruited recently (180 days prior to randomisation) symptomatic patients with carotid stenosis greater than 70% on carotid ultrasound (equivalent to greater than 50% by NASCET criteria). As in EVA-3S, patient had to have made a useful recovery from their stroke, expressed by a modified Rankin score of less than 3. Surgeons had to have the experience of at least 25 carotid endarterectomies and interventionists were required to show proof of 25 successful angioplasty or stent procedures.

#### Method of Randomisation

Two trials (CAVATAS and CAVATAS-MED) used the randomisation service at the Clinical Trial Service Unit in Oxford, UK to randomly assign patients to either treatment group. A computerised minimisation algorithm was used that took into account centre and timing of symptoms.

Wallstent used a computerised number-generator for randomisation. Assignment to treatment was provided in sequentially numbered sealed envelopes. Each centre was assigned its own randomisation sequence.

In the Leicester study patients were assigned to treatment on a consecutive basis from 300 random treatment methods numbered and sealed opaque envelopes. Sealed envelopes were also used for randomisation in BACASS.

An automated, centralised telephone response system was used for randomisation in SAPPHIRE while EVA-3S and SPACE used computer-based systems for randomly assigning treatment. In the case of EVA-3S this was a sequence involving randomised blocks of two, four, or six and in the case of SPACE a random allocation schedule.

The Chinese study of endovascular versus medical therapy used a random number table for randomisation but it was not entirely clear from the publication if treatment allocation was concealed.

The randomisation method in the above nine trials was considered to be adequate. In the remaining three trials no information regarding the method of randomisation was available and thus judged to be unclear.

Due to the nature of the interventions, it was not feasible to blind health workers, patients, or assessors to treatment or outcome in any of the trials.

#### Follow up

The formal follow up schedule differed between the different trials. CAVATAS and CAVATAS-MED followed up patients 30 days after treatment and then at 6 months, 12 months and yearly after randomisation. Follow up was carried out by an independent neurologist or clinician not directly involved in the actual trial treatment. The mean duration of follow up in CAVATAS was 1.95 years at the time of the original publication and 4.3 years in CAVATAS-MED. A similar follow up schedule was used in BACASS with follow up dates calculated from treatment date and provided a mean duration of follow up of 2 years. SPACE also followed up patients 30 days after treatment, at six months, one year and planned to conclude follow up two years after treatment.



SAPPHIRE followed the same schedule but the last follow up was conducted one year after treatment.

The Kentucky study of symptomatic patients had a more frequent follow up schedule with the first follow up taking place 48 hours after the procedure and again at one, three, six, 12, and 24 months. The asymptomatic Kentucky study used the same follow up schedule, plus an additional follow up visit 48 months after treatment.

EVA-3S also conducted the first follow up 48 hours after the procedure. The next follow up visits were then scheduled at 30 days, six months after treatment and every 6 months thereafter.

The first follow up was conducted even sooner in the Leicester and Wallstent studies 24 hours after treatment. In the Leicester study the next follow up was scheduled at 30 days and patients were followed up for two years, but the follow up intervals were not stated. Wallstent conducted a further follow up at six months, 12 months and annually thereafter.

TESCAS-C limited follow-up to 30 days and one year after treatment and the other Chinese study of endovascular versus medical treatment only reported results at 1.5 years after treatment.

#### Assessment of Functional Outcome

Only in five trials was the method of assessing functional outcome given in the relevant publications. The Leicester study used the Oxford Handicap Stroke score. The symptomatic Kentucky study and Wallstent used the Barthel score and modified Rankin scale to measure outcome. Wallstent and BACASS assessed functional outcome using the National Institute of Health Stroke Scale (NIHSS).

CAVATAS divided non-disabling strokes into those lasting fewer than seven days and those lasting for seven days or more. CAVATAS-MED included strokes of any duration.

If help was required to undertake activities of daily living for more than 30 days after the stroke it was classified as disabling.

In EVA-3S, SPACE, SAPPHIRE, Kentucky (asymptomatic trial), TESCAS-C, and the Chinese study of endovascular versus medical treatment, the method of assessing functional outcome was unspecified.

#### Analysis of Data

CAVATAS, CAVATAS-MED, BACASS and SPACE specified that data analyses were by intention to treat. EVA-3S analysed the 30-day results based on treatment received and the 6-months results by intention to treat. The Leicester study only reported results of patients who underwent treatment.

It was possible to extract the number of patients originally allocated to each treatment and the outcome of all patients from the publications for an intention-to-treat analysis.

SAPPHIRE included both symptomatic and asymptomatic patients and the majority of patients were in fact asymptomatic. Because it did not provide details of outcome events in asymptomatic patients it was not possible to analyse the symptomatic and asymptomatic patients separately.

**Table 10.1 – Cochrane Review: Summary of the characteristics of included studies**

*AF, atrial fibrillation; bd, twice daily; CEA, carotid endarterectomy; ICA, internal carotid artery; LOS, low output syndrome; LV, left ventricular; MI, myocardial infarction; NIH, National Institutes of Health; TIA, transient ischaemic attack.*

| Study  | Leicester 1998  |
|--------|---|
| Method | <p>Single centre, randomisation by sequentially numbered sealed opaque envelopes containing treatment methods</p> <p>2 patients randomised in the surgical arm were not included in the analysis: 1 patient spontaneously occluded the relevant ICA, the other patient refused to undergo treatment after admission</p> <p>4 patients in the endovascular group were not included in the analysis: 1 refused treatment after admission, the other 3 were awaiting admission for treatment when the trial was suspended</p> <p>Follow up at 24 hours and 30 days</p> |

|                               |  |
|-------------------------------|--|
| <b>Participants</b>           | <p>23 patients with symptomatic carotid stenosis of 70% to 99% assigned to optimal medical treatment with either CEA or carotid angioplasty and stenting</p> <p>Patients with asymptomatic disease, symptomatic 0% to 69% stenosis, crescendo TIA or stroke in evolution and vertebrobasilar or non-hemispheric symptoms were excluded</p>   |
| <b>Interventions</b>          | <p>Patients assigned to CEA or carotid angioplasty and stenting</p> <p>Aspirin therapy was not stopped before treatment</p> <p>All patients received intravenous heparin at the time of the procedure</p> <p>In addition, any patient with evidence of more than 25 emboli during any 10 minute period of transcranial doppler monitoring was given an incremental intravenous infusion of dextran 40</p>  |
| <b>Outcomes</b>               | <p>Death and ipsilateral stroke at 30 days post procedure</p> <p>Secondary outcome included median number of cerebral emboli detected on transcranial doppler</p>  |
| <b>Notes</b>                  | Terminated prematurely due to safety concerns  |
| <b>Allocation concealment</b> | A – Adequate   |
| <b>Study</b>                  | <b>CAVATAS 2001</b>  |
| <b>Method</b>                 | <p>Multicentre, central telephone randomisation</p> <p>Follow up at 1, 6, 12 months then annually by independent neurologist</p> <p>Intention-to-treat analysis</p>  |
| <b>Participants</b>           | <p>505 patients of any age with symptomatic or asymptomatic carotid artery stenosis suitable for surgery or endovascular treatment</p> <p>Patients unsuitable for surgery because of medical or surgical risk factors, who were unable to give informed consent, unwilling to undergo either procedure or if they had a disabling stroke with no useful recovery of function within the region supplied by the treatable artery were excluded</p> <p>40 patients with carotid artery stenosis who were not suitable for surgery were randomised to receive best medical treatment alone or in combination with endovascular treatment (see CAVATAS-MED 2007)</p> |
| <b>Interventions</b>          | <p>Patients fit for surgery assigned to endovascular treatment or CEA</p> <p>Those unfit for surgery assigned to endovascular treatment or medical care</p> <p>Patients in the endovascular group given minimum 150 mg aspirin daily for at least 24 hours prior to the procedure</p> <p>Heparin given at the time of procedure and for the following 24 hours</p>   |
| <b>Outcomes</b>               | <p>The primary outcome was specified as disabling stroke or death within 30 days of treatment</p> <p>The secondary outcome measure was ipsilateral stroke lasting more than 7 days</p>   |
| <b>Notes</b>                  |  |
| <b>Allocation concealment</b> | A – Adequate   |

|                               |  |
|-------------------------------|--|
| <b>Study</b>                  | <b>Kentucky (symptomatic) 2001</b>   |
| <b>Method</b>                 | Single centre, randomised (method not known)<br>Follow up at 1, 3, 6, 12 and 24 months   |
| <b>Participants</b>           | 104 patients with symptomatic carotid stenosis > 70% (events within 3 months of evaluation)<br><br>Patients with NIH score > 4, cardiac arrhythmia, sensitivity to aspirin, other antiplatelets or heparin or with recent intracranial haemorrhage were excluded   |
| <b>Interventions</b>          | Patients assigned to carotid angioplasty and stenting or surgery<br><br>All patients received 325 mg aspirin and 75 mg clopidogrel before the procedure and patients in the endovascular group received heparin at the time of the procedure   |
| <b>Outcomes</b>               | Death and stroke following the procedure<br><br>Secondary measures: restenosis rate, length of hospital stay, and relative costs of each procedure   |
| <b>Notes</b>                  |  |
| <b>Allocation concealment</b> | B – Unclear  |
| <b>Study</b>                  | <b>Wallstent 2001</b>  |
| <b>Method</b>                 | Multicentre, randomisation performed using a computerised random number generator, assignment by sequentially-numbered sealed envelopes; each centre assigned its own sequence   |
| <b>Participants</b>           | 219 patients aged > 18 years with symptomatic (> 60%) ICA stenosis with events in the last 120 days were included<br><br>Patients with ipsilateral arterial stenosis greater than the target lesion, NIH score > 15, Rankin score > 2, Barthel score < 60, AF, LV thrombus, endocarditis, heparin sensitivity, not suitable for surgery, moderate or severe dementia, bleeding diathesis or coagulopathy, history of intracranial haemorrhage were excluded  |
| <b>Interventions</b>          | Patients assigned to CEA or endovascular treatment<br><br>All patients in the endovascular group given aspirin 325 mg bd and ticlopidine 250 mg bd for 3 days prior to treatment<br><br>Following carotid angioplasty and stenting all patients treated with aspirin and ticlopidine for 4 weeks then aspirin only (325 mg bd)<br><br>For the CEA group use of ticlopidine was optional<br><br>All surgical patients were treated with aspirin 325 mg bd following the procedure for the duration of the study |
| <b>Outcomes</b>               | The primary endpoint for the study was the cumulative occurrence of any ipsilateral stroke, periprocedure death within 30 days or vascular death within one year of treatment<br><br>Secondary outcomes included time to major stroke, patency of the treated artery, time to contralateral stroke, time to death, and the occurrence of a TIA   |
| <b>Notes</b>                  | Terminated prematurely by the sponsor  |

|                        |   |
|------------------------|---|
| Allocation concealment | A – Adequate  |
| Study                  | <b>Beijing 2003</b>   |
| Method                 | Single centre, randomised by random number table<br>Follow up at 1.5 years after treatment  |
| Participants           | 21 patients with severe bilateral carotid stenosis  |
| Interventions          | Patients assigned to carotid stenting or medical care alone   |
| Outcomes               | Cerebrovascular symptoms since start of treatment   |
| Notes                  |   |
| Allocation concealment | B – Unclear   |
| Study                  | <b>Kentucky (asymptomatic) 2004</b>   |
| Method                 | Single centre, randomised (method not known)<br>Follow up at 1, 3, 6, 12, 24, and 48 months   |
| Participants           | 85 patients with asymptomatic carotid stenosis > 80% documented by digital subtraction angiography  |
| Interventions          | Patients assigned to carotid angioplasty and stenting or surgery<br>All patients received 325 mg aspirin and 75 mg clopidogrel before the procedure and patients in the endovascular group received heparin at the time of the procedure                                      |
| Outcomes               | Death and stroke following the procedure<br>Secondary measures: perception of perioperative pain, length of hospital stay, and relative costs of each procedure   |
| Notes                  |   |
| Allocation concealment | B – Unclear   |
| Study                  | <b>SAPPHIRE 2004</b>  |
| Method                 | Multicentre, randomisation by pseudo-random-number generator and distributed by an automated, centralised telephone response system   |
| Participants           | 334 patients with > 50% symptomatic carotid stenosis with one or more comorbidity criteria (i.e. high surgical risk group)  |
| Interventions          | Patients assigned to CEA or carotid stenting with cerebral protection<br>All patients received aspirin prior to and following treatment<br>In addition, the stented group received clopidogrel pre and post procedure<br>All patients were given heparin during the procedure |

|                               |   |
|-------------------------------|---|
| <b>Outcomes</b>               | Death, any stroke, and MI within 30 days of procedure<br>Death of ipsilateral stroke between 31 days and 1 year post procedure plus 30 day major adverse clinical event rate  |
| <b>Notes</b>                  | Terminated prematurely due to a drop in randomisation   |
| <b>Allocation concealment</b> | A – Adequate  |
| <b>Study</b>                  | <b>BACASS 2006</b>  |
| <b>Method</b>                 | Single centre, randomised by sealed envelopes<br>Follow up at 1, 6, 12 months and yearly thereafter conducted between 1998 and 2002   |
| <b>Participants</b>           | 20 patients with symptomatic carotid stenosis > 70%<br>Patients were excluded if they were unwilling to participate, unavailable for at least 2 years for follow up, or presented with ICA occlusion or free floating thrombus  |
| <b>Interventions</b>          | Patients were assigned to either stenting or CEA  |
| <b>Outcomes</b>               | Primary outcome measures were periprocedural stroke, death or MI<br>Secondary outcome measures were peri-interventional TIA, haematoma, cranial nerve paralysis and LOS<br>For the follow up, secondary outcome measures were patency of the treated vessel and stroke prevention related to the treated side                     |
| <b>Notes</b>                  |   |
| <b>Allocation concealment</b> | A – Adequate  |
| <b>Study</b>                  | <b>SPACE 2006</b>   |
| <b>Method</b>                 | Multicentre, randomised by computer-generated random allocation schedule<br>Follow up at 7 and 30 days, and after 6, 12, and 24 months  |
| <b>Participants</b>           | 1,183 patients with symptomatic carotid stenosis > 70% on duplex ultrasound in the previous 180 days of enrolment<br>Patients had to be older than 50 years   |
| <b>Interventions</b>          | Patients assigned to stenting or CEA, patients had to be treated within 14 days of randomisation<br>All patients in the stenting group had to be given 100 mg aspirin plus 75 mg clopidogrel daily for 3 days before and 30 days after treatment<br>CEA patients had to be given 100 mg aspirin before, during, and after surgery |

|                               |  |
|-------------------------------|--|
| <b>Outcomes</b>               | <p>Ipsilateral stroke or death of any cause between randomisation and 30 days after treatment</p> <p>Disabling ipsilateral stroke or death from any cause since randomisation</p> <p>Any stroke up to days after treatment</p> <p>Procedural failure including inability to treat with allocated technique, remaining stenosis &gt; 50% or vessel occlusion assessed up to 30 days after treatment</p> |
| <b>Notes</b>                  | Terminated prematurely after futility analysis   |
| <b>Allocation concealment</b> | A – Adequate   |
| <b>Study</b>                  | <b>EVA-3S 2006</b>   |
| <b>Method</b>                 | <p>Multicentre, randomisation by computer-generated sequence, involving randomised blocks of 2, 4, or 6</p> <p>Patients stratified by centre and degree of stenosis</p> <p>Follow up at 48 hours, 30 days and 6 months after treatment</p>   |
| <b>Participants</b>           | <p>527 patients with symptomatic carotid stenosis between 60% and 99% within 120 days before enrolment</p> <p>Patients had to be fit to undergo either surgery or stenting</p> <p>Patients with Rankin score &gt; 3, severe tandem lesions, previous revascularisation of the symptomatic stenosis were excluded</p>   |
| <b>Interventions</b>          | <p>Patients assigned to stenting or surgery</p> <p>After the study was started, use of cerebral protection devices became mandatory in the stenting group</p> <p>It was recommended to use between 100 mg and 300 mg of aspirin daily in all patients, and 75 mg clopidogrel or 500 mg ticlopidine for 3 days before and 30 days after stenting</p>  |
| <b>Outcomes</b>               | <p>Any stroke or death within 30 days after treatment</p> <p>MI, TIA, cranial nerve injury, major local complications, and systemic complications within 30 days after treatment</p> <p>Any stroke or death within 30 days of treatment plus ipsilateral stroke, any stroke, or any stroke or death within 31 days through end of follow up</p>  |
| <b>Notes</b>                  | Study terminated prematurely due to safety and futility concerns   |
| <b>Allocation concealment</b> | A – Adequate   |
| <b>Study</b>                  | <b>TESCAS-C 2006</b>   |
| <b>Method</b>                 | <p>Multicentre, randomised (method not known)</p> <p>Follow up at 1 and 6 months</p>   |
| <b>Participants</b>           | 166 patients with severe symptomatic or asymptomatic carotid stenosis  |
| <b>Interventions</b>          | Patients assigned to carotid stenting or CEA   |

|                               |   |
|-------------------------------|---|
| <b>Outcomes</b>               | Death, stroke or MI at 30 days after treatment<br>Death or ipsilateral stroke between 31 days and 6 months after treatment  |
| <b>Notes</b>                  | Publication in Chinese with English abstract only, data presented in review taken from abstract   |
| <b>Allocation concealment</b> | B – Unclear   |
| <b>Study</b>                  | <b>CAVATAS-MED 2007</b>   |
| <b>Method</b>                 | Trial methods were the same as in CAVATAS-CEA 2001  |
| <b>Participants</b>           | 40 patients with carotid artery stenosis who were not suitable for surgery were randomised to receive best medical treatment alone or in combination with endovascular treatment  |
| <b>Interventions</b>          | Patients were assigned to receive either endovascular or medical treatment<br>Patients in the endovascular group given minimum 150 mg aspirin daily for at least 24 hours prior to the procedure<br>Heparin given at the time of procedure and for the following 24 hours |
| <b>Outcomes</b>               | The primary outcome was specified as disabling stroke or death within 30 days of treatment<br>The secondary outcome measure was ipsilateral stroke lasting more than 7 days   |
| <b>Notes</b>                  |   |
| <b>Allocation concealment</b> | A – Adequate  |

### 10.3.5 Meta-analysis

#### Endovascular Treatment versus Carotid Endarterectomy

##### Safety

*Death or any stroke within 30 days after treatment*

Death or any stroke within 30 days after treatment was reported by eight trials. The  $\chi^2$ -test for heterogeneity did not suggest underlying heterogeneity ( $\chi^2 = 11.81$ ,  $p = 0.11$ ).

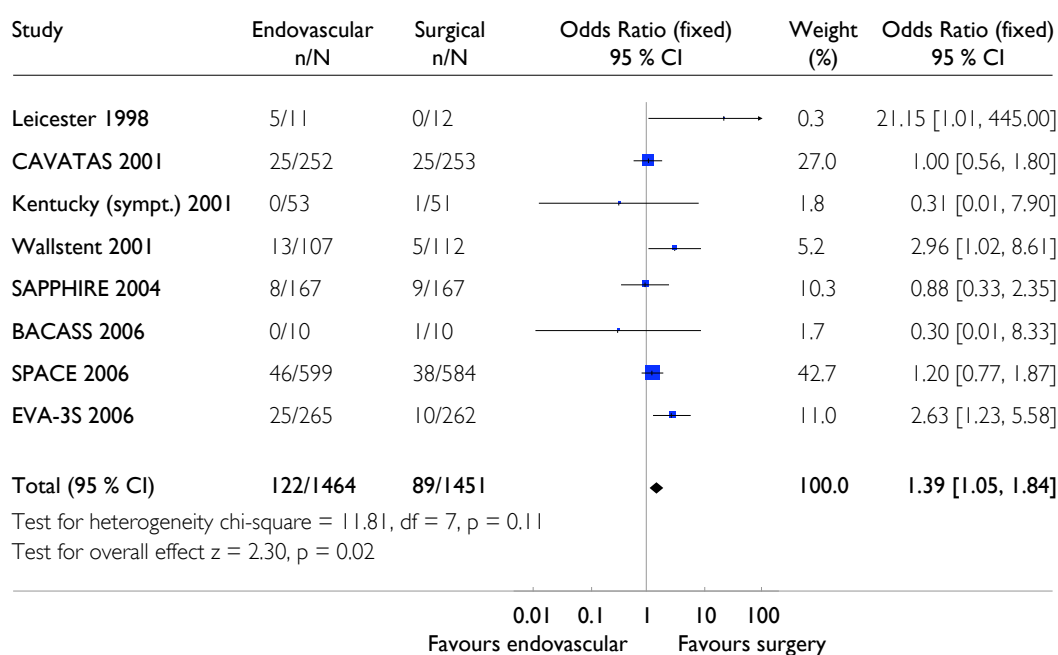
Death or any stroke was significantly more frequent in the endovascular treatment group using the fixed effect model (odds ratio [OR] 1.39, 95% CI 1.05 to 1.84,  $p = 0.02$ , Figure 10.1). The random effects model widened the 95% confidence interval and the statistical



significance disappeared (OR 1.44, 95% CI 0.91 to 2.26,  $p = 0.12$ , see Appendix for forest plots of all random effects model calculations).

**Figure 10.1 – Cochrane Review: Meta-analysis of death or any stroke within 30 days after treatment in the fixed-effect model**

Odds ratio for death or any stroke within 30 days after treatment. The ends of the lines are the 95% CI. Analysis is based on published results. The large diamond represents the odds ratio and 95% CI of the combined data. The summary estimate statistic is calculated using a Mantel-Haenszel fixed-effect model, the centre of the diamond is the point estimate, and its width the 95% CI. The  $\chi^2$  test indicates the strength of evidence for heterogeneity. N, number of patients in each treatment group; n, number of events; CI, confidence interval; df, degrees of freedom.

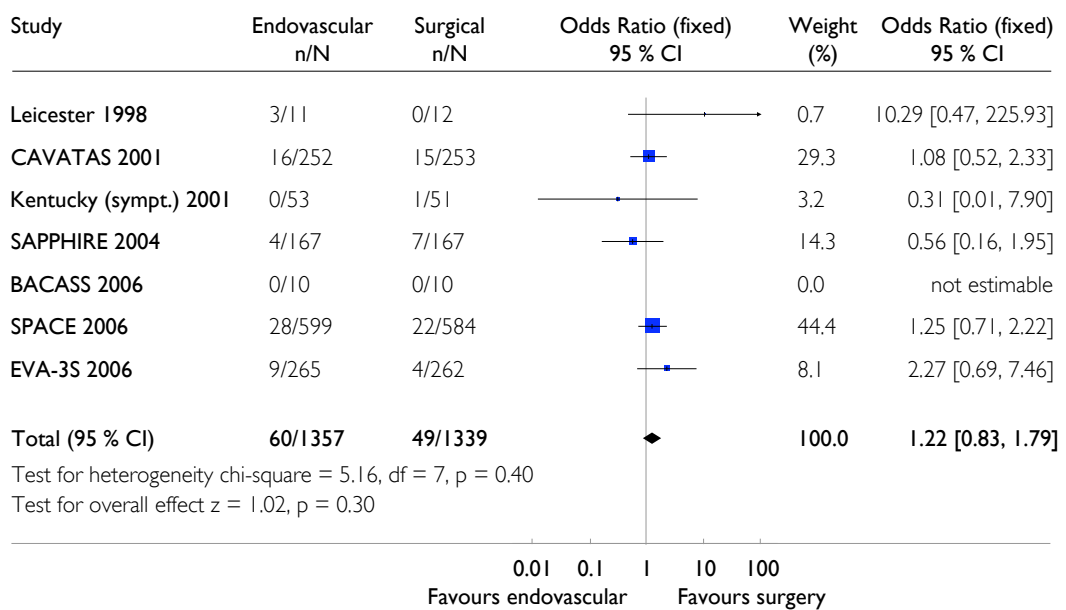


Death or disabling stroke within 30 days after treatment

Only seven trials distinguished between disabling and non-disabling stroke and no significant heterogeneity among trials was suggested ( $\chi^2 = 5.16$ ,  $p = 0.40$ ). Disabling stroke or death was more frequent following endovascular treatment, but this result was statistically significant neither using the fixed effect model (OR 1.22, 95% CI 0.83 to 1.79,  $p = 0.31$ , Figure 10.2) nor in the random effects model (OR 1.20, 95% CI 0.80 to 1.80,  $p = 0.39$ ).

**Figure 10.2 – Cochrane Review: Meta-analysis of disabling stroke or death within 30 days after treatment in the fixed-effect model**

Odds ratio for disabling stroke or death within 30 days after treatment. The ends of the lines are the 95% CI. Analysis is based on published results. The large diamond represents the odds ratio and 95% CI of the combined data. The summary estimate statistic is calculated using a Mantel-Haenszel fixed-effect model, the centre of the diamond is the point estimate, and its width the 95% CI. The  $\chi^2$  test indicates the strength of evidence for heterogeneity. N, number of patients in each treatment group; n, number of events; CI, confidence interval; df, degrees of freedom.

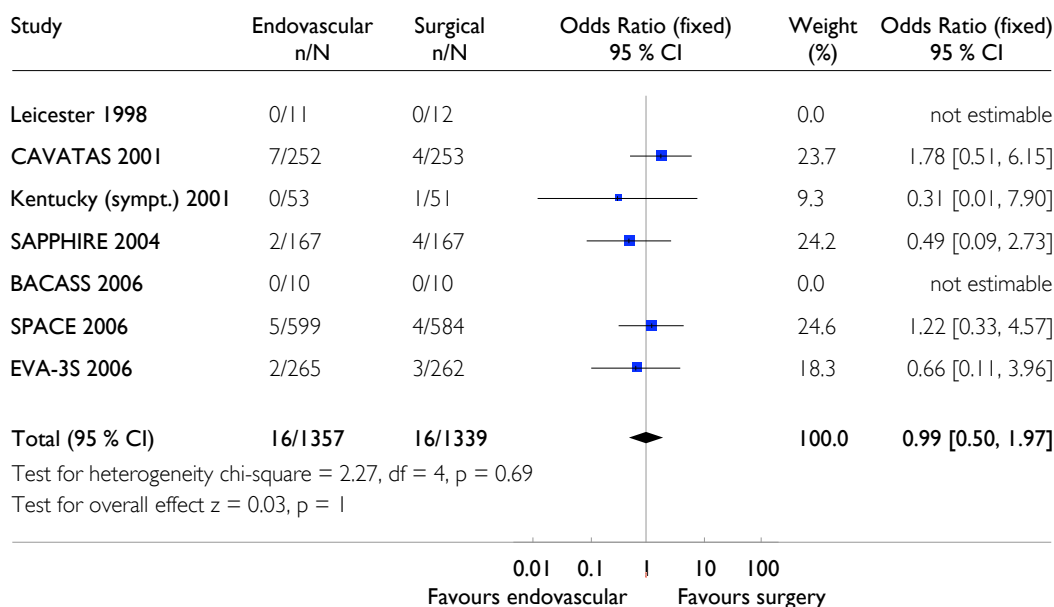


### Death within 30 days after treatment

No significant heterogeneity among the seven trials reporting death within 30 days after treatment ( $\chi^2 = 2.27$ ,  $p = 0.69$ ). The risk of death was not different in either treatment group using both the fixed effect model (OR 0.99, 95% CI 0.50 to 1.97,  $p = 0.98$ , Figure 10.3) and the random effects model (OR 1.00, 95% CI 0.49 to 2.04,  $p = 0.99$ ).

**Figure 10.3 – Cochrane Review: Meta-analysis of death within 30 days after treatment in the fixed-effect model**

Odds ratio for death within 30 days after treatment. The ends of the lines are the 95% CI. Analysis is based on published results. The large diamond represents the odds ratio and 95% CI of the combined data. The summary estimate statistic is calculated using a Mantel-Haenszel fixed-effect model, the centre of the diamond is the point estimate, and its width the 95% CI. The  $\chi^2$  test indicates the strength of evidence for heterogeneity. N, number of patients in each treatment group; n, number of events; CI, confidence interval; df, degrees of freedom.

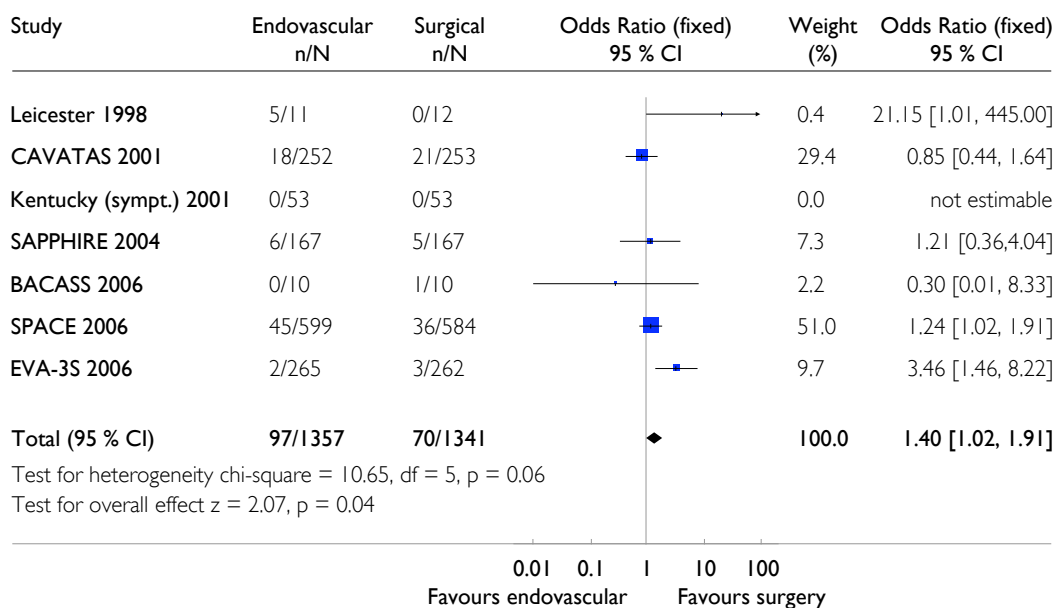


### Stroke within 30 days after treatment

The same seven trials showed a significantly different effect for stroke within 30 days after treatment in favour of carotid endarterectomy. The fixed effect model's odds ratio was 1.40 (95% CI 1.02 to 1.91,  $p = 0.04$ , Figure 10.4). However, there was significant heterogeneity among the trials ( $\chi^2 = 10.65$ ,  $p = 0.06$ ) and using the random effects model widened the confidence interval and rendered the result not statistically significant (OR 1.47, 95% CI 0.81 to 2.67,  $p = 0.20$ ).

**Figure 10.4 – Cochrane Review: Meta-analysis of stroke within 30 days after treatment in the fixed-effect model**

Odds ratio for any stroke within 30 days after treatment. The ends of the lines are the 95% CI. Analysis is based on published results. The large diamond represents the odds ratio and 95% CI of the combined data. The summary estimate statistic is calculated using a Mantel-Haenszel fixed-effect model, the centre of the diamond is the point estimate, and its width the 95% CI. The  $\chi^2$  test indicates the strength of evidence for heterogeneity. N, number of patients in each treatment group; n, number of events; CI, confidence interval; df, degrees of freedom.

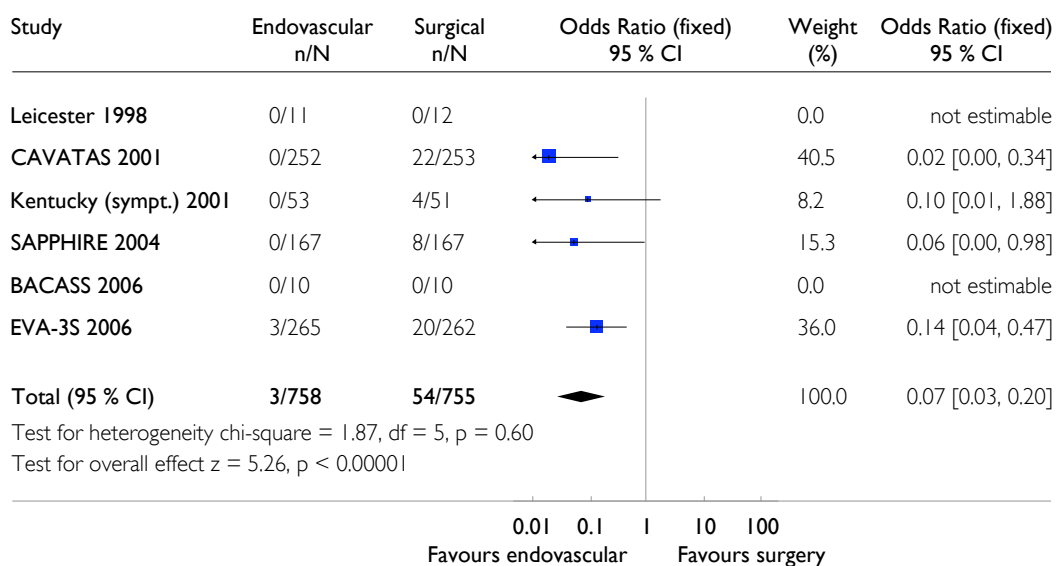


### Cranial neuropathy within 30 days after treatment

The rate of cranial neuropathy within 30 days after treatment was reported in six trials without significant heterogeneity among the studies ( $\chi^2 = 1.87$ ,  $p = 0.60$ ). The result significantly favoured endovascular treatment using both the fixed effect model (OR 0.07, 95% CI 0.03 to 0.20,  $p < 0.00001$ ) and the random effects model (OR 0.09, 95% CI 0.04 to 0.25,  $p < 0.00001$ , Figure 10.5).

**Figure 10.5 – Cochrane Review: Meta-analysis of cranial neuropathy within 30 days after treatment in the fixed-effect model**

Odds ratio for cranial neuropathy within 30 days after treatment. The ends of the lines are the 95% CI. Analysis is based on published results. The large diamond represents the odds ratio and 95% CI of the combined data. The summary estimate statistic is calculated using a Mantel-Haenszel fixed-effect model, the centre of the diamond is the point estimate, and its width the 95% CI. The  $\chi^2$  test indicates the strength of evidence for heterogeneity. N, number of patients in each treatment group; n, number of events; CI, confidence interval; df, degrees of freedom.

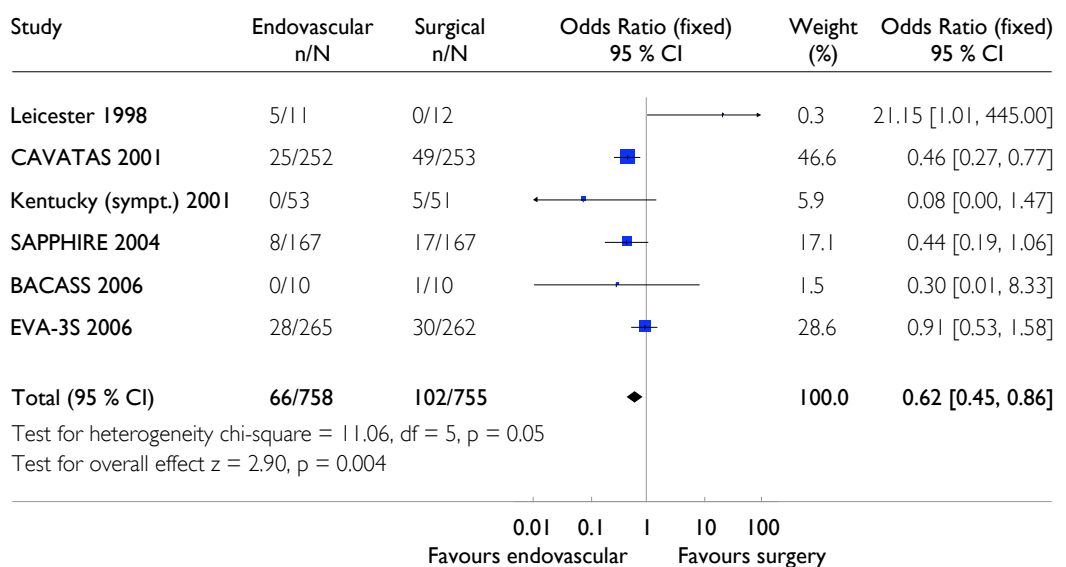


# Death or neurological complications within 30 days after treatment

Data from six trials were available that allowed for death and neurological complications (stroke and cranial neuropathy) to be combined. This combined outcome significantly favoured endovascular treatment in the fixed effect model (OR 0.62, 95% CI 0.45 to 0.86,  $p = 0.004$ , Figure 10.6). However, there was significant heterogeneity among the included trials ( $\chi^2 = 11.06$ ,  $p = 0.05$ ) and the random effects model produced a non-significant result in favour of endovascular treatment (OR 0.60, 95% CI 0.31 to 1.17,  $p = 0.13$ ).

**Figure 10.6 – Cochrane Review: Meta-analysis of death or neurological complications within 30 days after treatment in the fixed-effect model**

Odds ratio for death or neurological complications (cranial neuropathy, stroke) within 30 days after treatment. The ends of the lines are the 95% CI. Analysis is based on published results. The large diamond represents the odds ratio and 95% CI of the combined data. The summary estimate statistic is calculated using a Mantel-Haenszel fixed-effect model, the centre of the diamond is the point estimate, and its width the 95% CI. The  $\chi^2$  test indicates the strength of evidence for heterogeneity. N, number of patients in each treatment group; n, number of events; CI, confidence interval; df, degrees of freedom.

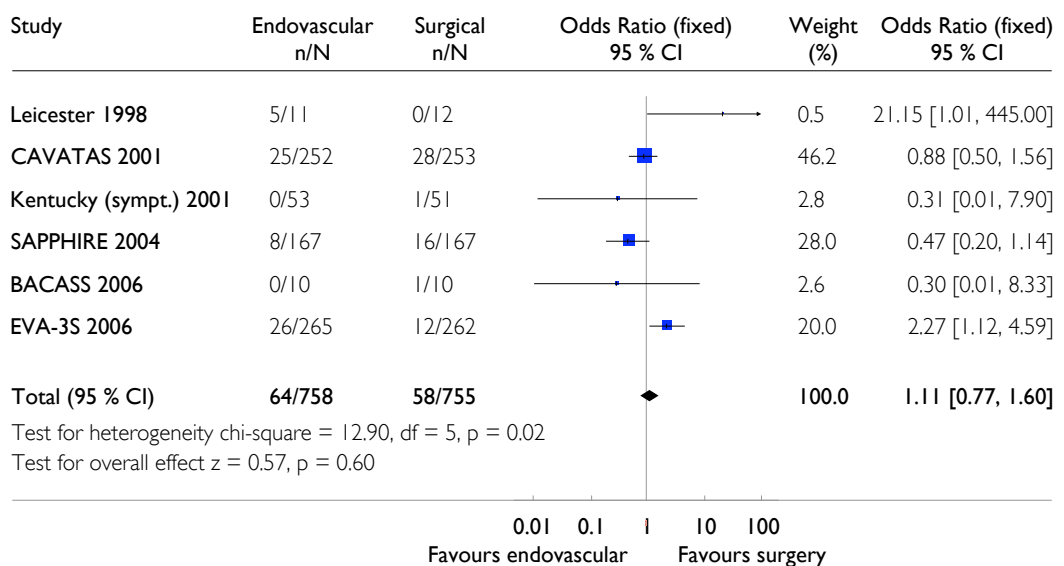


# Death or stroke or myocardial infarction within 30 days after treatment

Six trials allowed for combining death, stroke and myocardial infarction in one outcome measure. No significant difference was found between treatments in both the fixed effect model (OR 1.11, 95% CI 0.77 to 1.60,  $p = 0.57$ ) and the random effects model (OR 1.06, 95% CI 0.48 to 2.38,  $p = 0.88$ , Figure 10.7). There was significant heterogeneity among trials ( $\chi^2 = 12.90$ ,  $p = 0.02$ ).

**Figure 10.7 – Cochrane Review: Meta-analysis of death or stroke or myocardial infarction within 30 days after treatment in the fixed-effect model**

Odds ratio for death or stroke or myocardial infarction within 30 days after treatment. The ends of the lines are the 95% CI. Analysis is based on published results. The large diamond represents the odds ratio and 95% CI of the combined data. The summary estimate statistic is calculated using a Mantel-Haenszel fixed-effect model, the centre of the diamond is the point estimate, and its width the 95% CI. The  $\chi^2$  test indicates the strength of evidence for heterogeneity. N, number of patients in each treatment group; n, number of events; CI, confidence interval; df, degrees of freedom.

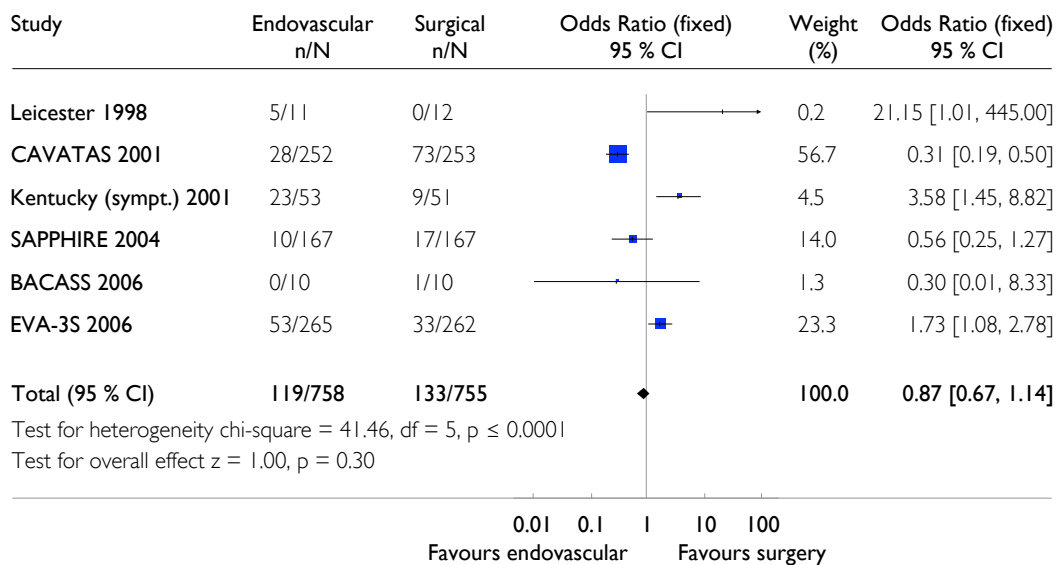


Death, stroke, cranial neuropathy or myocardial infarction within 30 days after treatment

The same six studies were combined for analysing death, stroke, cranial neuropathy and myocardial infarction in one outcome measure. While there was significant heterogeneity among the trials (OR 41.46,  $p < 0.00001$ ), little difference was found between endovascular treatment and endarterectomy in both the fixed effect model (OR 0.87, 95% CI 0.67 to 1.14,  $p = 0.32$ , Figure 10.8) and the random effects model (OR 1.16, 95% CI 0.41 to 3.24,  $p = 0.78$ ).

**Figure 10.8 – Cochrane Review: Meta-analysis of death, stroke, cranial neuropathy or myocardial infarction within 30 days after treatment in the fixed-effect model**

Odds ratio for death, stroke, cranial neuropathy or myocardial infarction within 30 days after treatment. The ends of the lines are the 95% CI. Analysis is based on published results. The large diamond represents the odds ratio and 95% CI of the combined data. The summary estimate statistic is calculated using a Mantel-Haenszel fixed-effect model, the centre of the diamond is the point estimate, and its width the 95% CI. The  $\chi^2$  test indicates the strength of evidence for heterogeneity. N, number of patients in each treatment group; n, number of events; CI, confidence interval; df, degrees of freedom.





## Efficacy

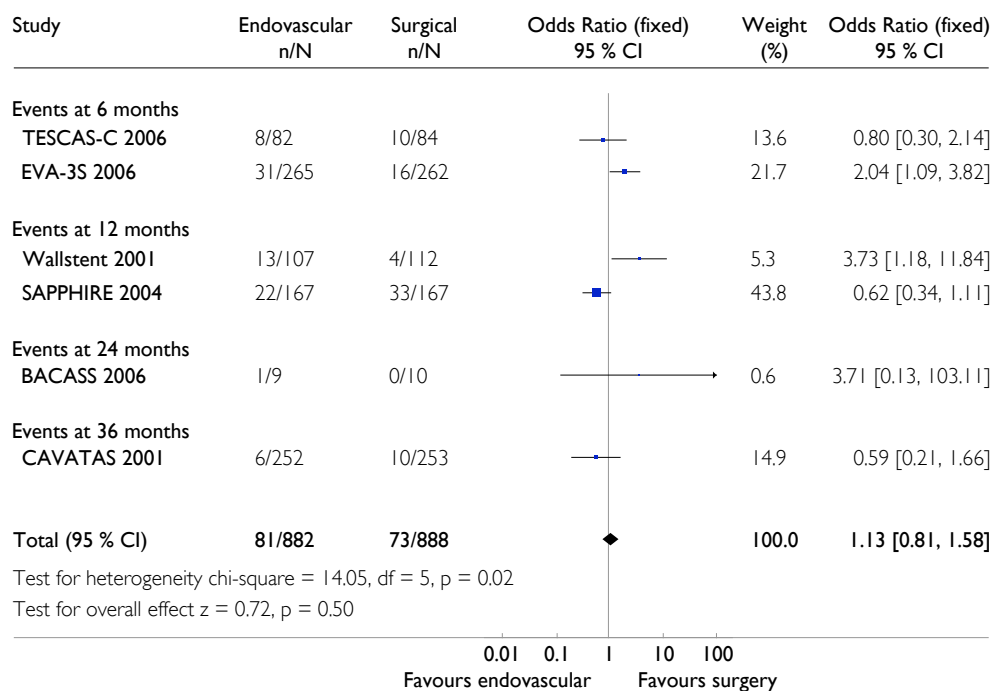
Long-term efficacy was difficult to assess because trials reported outcome after different time intervals. Two trials reported six months' results, two trials reported outcome events 12 months after randomisation and one trial each presented results after 2 and after 3 years of follow up.

*Death or any stroke during follow-up, including the initial 30-day post treatment period*

Heterogeneity among the six trials reporting death or stroke during follow up was significant ( $\chi^2 = 14.05$ ,  $p = 0.02$ ). Discounting different lengths of follow up, the excess of death or stroke during follow up in the endovascular treatment group was not statistically significant in the fixed effect model (OR 1.13, 95% CI 0.81 to 1.58,  $p = 0.47$ , Figure 10.9) and the random effects model (OR 1.18, 95% CI 0.61 to 2.28,  $p = 0.62$ ).

**Figure 10.9 – Cochrane Review: Meta-analysis of death or stroke during follow-up in the fixed-effect model**

Odds ratio for death or stroke during follow up, including the 30-day post-treatment period. The ends of the lines are the 95% CI. Analysis is based on published results. The large diamond represents the odds ratio and 95% CI of the combined data. The summary estimate statistic is calculated using a Mantel-Haenszel fixed-effect model, the centre of the diamond is the point estimate, and its width the 95% CI. The  $\chi^2$  test indicates the strength of evidence for heterogeneity. N, number of patients in each treatment group; n, number of events; CI, confidence interval; df, degrees of freedom.

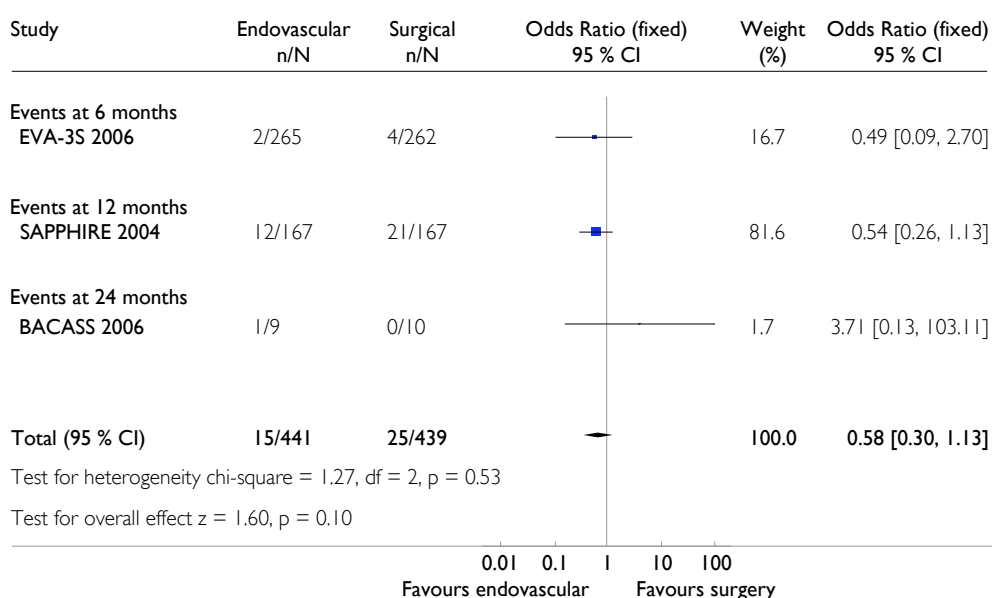


# Death occurring later than 30 days after treatment

Three trials provided data on death occurring more than 30 days after treatment and there was no significant heterogeneity among these trials ( $\chi^2 = 1.27$ ,  $p = 0.53$ ). Neither the fixed effect model (OR 0.58, 95% CI 0.30 to 1.13,  $p = 0.11$ , Figure 10.10) nor the random effects model (OR 0.57, 95% CI 0.29 to 1.12,  $p = 0.53$ ) revealed a significant difference between treatments.

**Figure 10.10 – Cochrane Review: Meta-analysis of death occurring more than 30 days after treatment in the fixed-effect model**

Odds ratio for death occurring more than 30 days after treatment. The ends of the lines are the 95% CI. Analysis is based on published results. The large diamond represents the odds ratio and 95% CI of the combined data. The summary estimate statistic is calculated using a Mantel-Haenszel fixed-effect model, the centre of the diamond is the point estimate, and its width the 95% CI. The  $\chi^2$  test indicates the strength of evidence for heterogeneity. N, number of patients in each treatment group; n, number of events; CI, confidence interval; df, degrees of freedom.

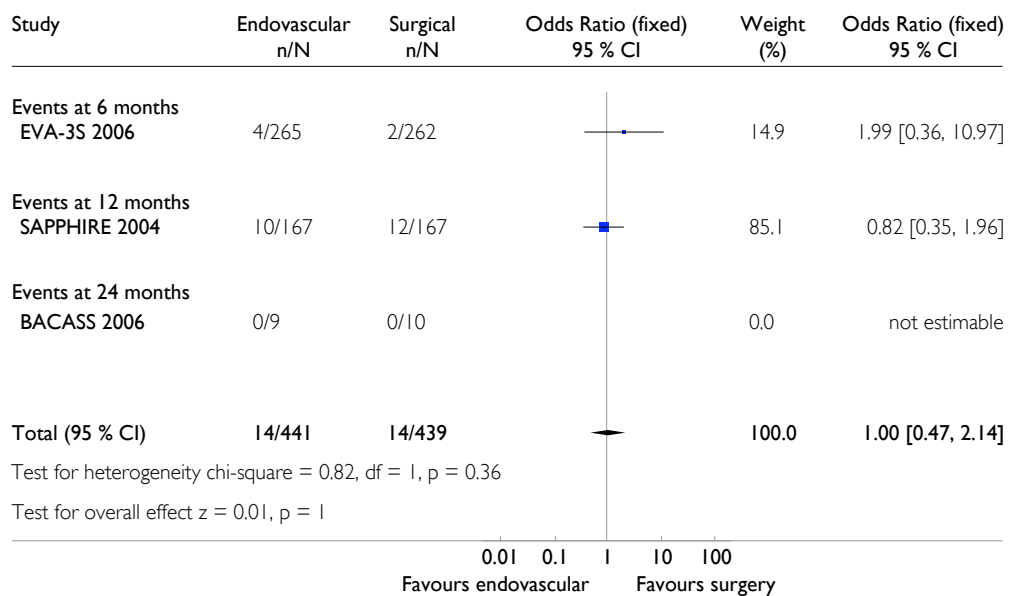


### Stroke occurring later than 30 days after treatment

The effect for stroke occurring later than 30 days after treatment in the same three trials was significantly different in neither the fixed effect (OR 1.00, 95% CI 0.47 to 2.14,  $p = 0.99$ , Figure 10.11) nor the random effects model (OR 0.99, 95% CI 0.46 to 2.14,  $p = 1.00$ ). No significant heterogeneity among trials was detected ( $\chi^2 = 0.82$ ,  $p = 0.36$ ).

**Figure 10.11 – Cochrane Review: Meta-analysis of stroke occurring more than 30 days after treatment in the fixed-effect model**

Odds ratio stroke occurring more than 30 days after treatment. The ends of the lines are the 95% CI. Analysis is based on published results. The large diamond represents the odds ratio and 95% CI of the combined data. The summary estimate statistic is calculated using a Mantel-Haenszel fixed-effect model, the centre of the diamond is the point estimate, and its width the 95% CI. The  $\chi^2$  test indicates the strength of evidence for heterogeneity. N, number of patients in each treatment group; n, number of events; CI, confidence interval; df, degrees of freedom.



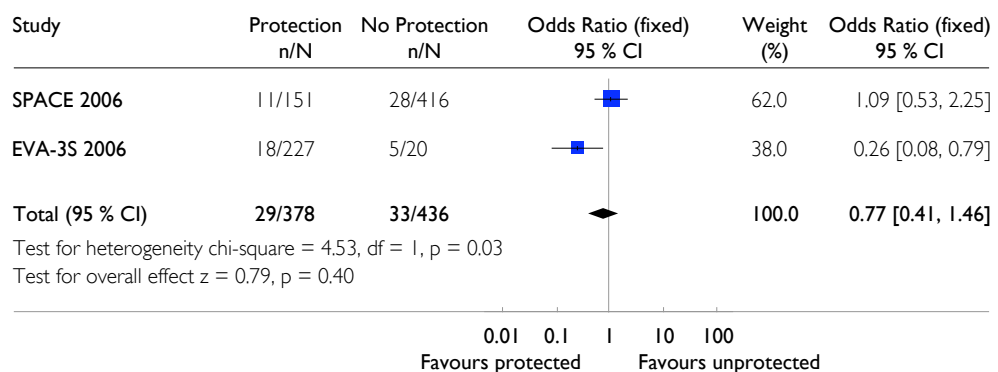
## Protected versus Unprotected Endovascular Treatment

*Death or stroke within 30 days after treatment*

Data from two trials were obtainable to compare endovascular treatment with and without cerebral protection devices, with significant heterogeneity between trials ( $\chi^2 = 4.53$ ,  $p = 0.03$ ). The use of protection devices was not favoured statistically significant in either the fixed effect (OR 0.77, 95% CI 0.41 to 1.46,  $p = 0.43$ , Figure 10.12) or random effects model (OR 0.57, 95% CI 0.14 to 2.33,  $p = 0.43$ ).

**Figure 10.12 – Cochrane Review: Meta-analysis of protected versus unprotected endovascular treatment in the fixed-effect model**

Odds ratio for protected versus unprotected endovascular treatment. The ends of the lines are the 95% CI. Analysis is based on published results. The large diamond represents the odds ratio and 95% CI of the combined data. The summary estimate statistic is calculated using a Mantel-Haenszel fixed-effect model, the centre of the diamond is the point estimate, and its width the 95% CI. The  $\chi^2$  test indicates the strength of evidence for heterogeneity. N, number of patients in each treatment group; n, number of events; CI, confidence interval; df, degrees of freedom.



### 10.3.6 Endovascular Treatment versus Carotid Endarterectomy in Asymptomatic patients

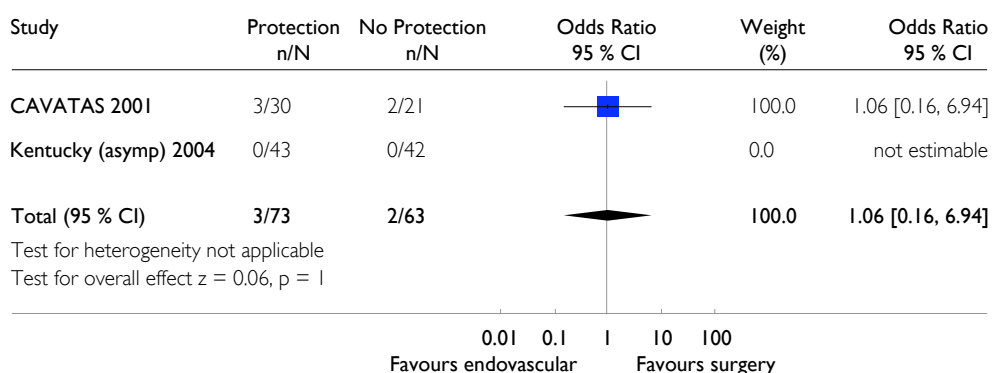
Three trials allowed for asymptomatic patients to be included in the study according to their study protocol. However, in only two trials, the number of asymptomatic patients and corresponding event rate was available for analysis in this Cochrane review.

*Death or stroke within 30 days after treatment*

Death or stroke only occurred in one trial. There was no difference between endovascular treatment and carotid endarterectomy and the fixed effect and random effects model both produced the same odds ratio (OR 1.06, 95% CI 1.06 to 6.94,  $p = 0.96$ , Figure 10.13).

**Figure 10.13 – Cochrane Review: Meta-analysis of death or stroke within 30 days after treatment in asymptomatic patients**

Odds ratio for death or stroke within 30 days after treatment in asymptomatic patients. The end of the lines are the 95% CI. Analysis is based on published results. The large diamond represents the odds ratio and 95% CI of the combined data. The summary estimate statistic is a Mantel-Haenszel (fixed-effect model), the centre of the diamond is the point estimate, and its width the 95% CI. The  $\chi^2$  test indicates the strength of evidence for heterogeneity. N, number of patients in each treatment group; n, number of events; CI, confidence interval; df, degrees of freedom.



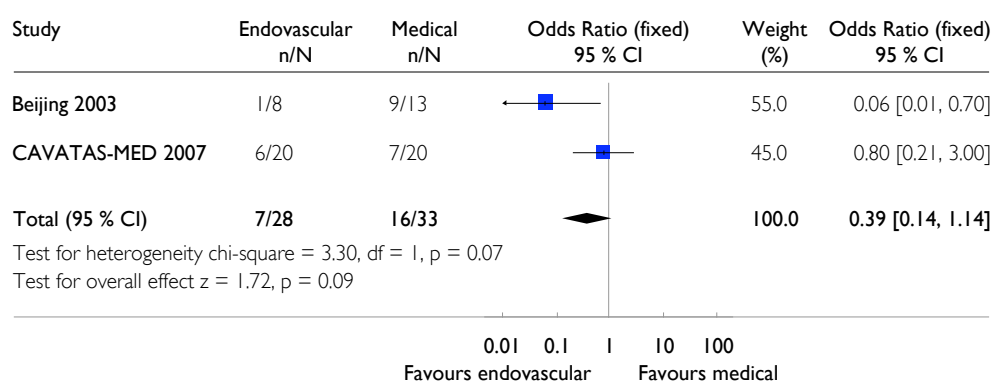
## Endovascular Treatment versus Medical Care

*Death or stroke occurring later than 30 days after treatment/randomisation*

Only the results of two very small trials were available for the analysis of death or stroke occurring later than 30 days after treatment or randomisation and heterogeneity between these two trials was significant ( $\chi^2 = 3.30$ ,  $p = 0.07$ ). And neither the fixed effect model (OR 0.39, 95% CI 0.14 to 1.14,  $p = 0.09$ , Figure 10.14) nor the random effects model (OR 0.28, 95% CI 0.02 to 3.23,  $p = 0.30$ ) significantly favoured endovascular treatment over medical management alone.

**Figure 10.14 – Cochrane Review: Meta-analysis of death or stroke occurring later than 30 days after endovascular treatment or randomisation in the fixed-effect model**

Odds ratio for death or stroke occurring more than 30 days after endovascular treatment or randomisation. The ends of the lines are the 95% CI. Analysis is based on published results. The large diamond represents the odds ratio and 95% CI of the combined data. The summary estimate statistic is calculated using a Mantel-Haenszel fixed-effect model, the centre of the diamond is the point estimate, and its width the 95% CI. The  $\chi^2$  test indicates the strength of evidence for heterogeneity. N, number of patients in each treatment group; n, number of events; CI, confidence interval; df, degrees of freedom.



## Other Outcome Comparisons

### Restenosis

It was planned to analyse the rate of restenosis. However, the degree of residual stenosis or restenosis at one year was only available from CAVATAS and BACASS. CAVATAS found ipsilateral carotid stenosis between 70% and 99% to be more frequent following endovascular treatment than after endarterectomy (14% compared to 4%,  $p < 0.001$ ) but

the rate of ipsilateral stroke in the survival analysis up to 3 years after randomisation was not significantly different. BACASS reported one patient in each treatment arm with a restenosis between 30% and 49% and one patient in the surgery group with a stenosis between 50% and 69% at the time of the 2-year follow up.

The Kentucky study in symptomatic patients reported that the patency of treated arteries remained 'acceptable' two years after treatment in both groups but did not provide specific restenosis rates nor did it define 'acceptable'.

Source of heterogeneity and learning curve

Not enough individual patient data were available to further investigate the source of heterogeneity among trials. The analysis of a potential learning curve in carotid stenting was not able to proceed because of a lack of individual patient data.

No information regarding ipsilateral stroke during long term follow up was extractable from the individual trial publications and this analysis was therefore not carried out.

#### **10.3.7 Discussion of Results**

This review and meta-analysis of randomised clinical trials showed a significant difference in the risk of stroke or death between patients treated endovascularly and those patients treated with surgery using the fixed effect model, favouring carotid endarterectomy. There was no difference in the risk of death between the two treatment groups and the increase in risk of death or stroke was primarily driven by the difference in the risk of stroke. However, using the random effects model to calculate the odds ratio led to a widening of the 95% confidence interval and rendered the difference in risk not statistically significant. This suggests that the results of this analysis are not very robust. Most likely the number of patients and events in each treatment group are not sufficient to provide a robust estimate of the overall risk difference.

No significant difference in the risk of death or disabling stroke within 30 days after treatment were found, suggesting that non-disabling stroke are the driving force behind

any difference between endovascular treatment and carotid endarterectomy, although this specific analysis was not possible due to lack of information in the individual trial publications.

Centres taking part in the randomised trials had a specific interest in secondary prevention of stroke and care must be taken when extrapolating the data into routine clinical practice in less specialist centres. Furthermore, three of the included trials were stopped early because of an excess event rate in the endovascular treatment group. Therefore, the overall result might well be biased because of this. This fact needs to be kept in mind when interpreting the results of the meta-analysis.

Little doubt remains about the significant reduction in peri-procedural cranial neuropathy in patients undergoing endovascular treatment compared to those who underwent carotid endarterectomy. Potentially, cranial neuropathy can have a devastating impact on the quality of life of affected patients. It may require the placement of a percutaneous endogastric tube or greatly impair speech. It is difficult to adequately take cranial neuropathy into account when balancing the risks and benefits of endovascular treatment over carotid endarterectomy. While including cranial neuropathy in a combined outcome measure together with death and stroke off-set the increased risk of stroke after endovascular treatment and tended to favour endovascular, adding myocardial infarction to this outcome showed no significant difference between the treatments. This was because of an increase in myocardial infarction in the endovascular treatment group.

Only one of the trials included in this review concluded from their individual results that endovascular treatment was not inferior to carotid endarterectomy. All other trials were much more cautious in the interpretation of safety data and either concluded that carotid endarterectomy was the safer option or that not sufficient evidence would justify a shift of clinical practice away from carotid endarterectomy as the treatment of choice of symptomatic carotid stenosis. This view has to be supported by the meta-analysis that



overall showed a tendency towards carotid endarterectomy being superior to endovascular treatment in short term outcome, but the number of patients and the number of observed events was too small to provide a robust estimate of the overall odds ratio.

At the time of this review very little information about long term efficacy of endovascular treatment compared to endarterectomy was available and only 4 trials provided at least 1-year follow up data and the reported length of follow up differed greatly. There appears to be consensus in the carotid stenosis research community what the important short-term outcome data are. The initial 30 days after treatment have been identified as of particular interest and the vast majority of trials report this data and are also surprisingly consistent in their selection of outcome measures for this time period.

Unfortunately, there is a complete breakdown in consensus beyond the 30-day safety period. The reported outcome measures are as numerous as there are trials and the trial publications make it very difficult to identify outcome measures that all trials have in common without the knowledge of individual patient data. But not only do long-term outcome measures differ, there is also no uniformity on the length of reported follow up. Most likely, this lack of consistency in reporting is owed to funding since it is quite expensive to keep a trial running for a long period of time. However, the question must be allowed, why trialists ignore previous publications in their field and do not report the same outcome events, even if their trials provide longer follow up. This could be easily done in addition to their own pre-specified analyses and would make comparison of trials much easier.

On this basis it is very difficult to form a firm conclusion about the long-term efficacy of treatment. It appears that the effects of death and stroke during follow up are very similar beyond the initial 30-day peri-procedural period. And the overall differences between endovascular treatment and endarterectomy appear to be determined by differences in the 30-day outcomes.

Cerebral filter devices are marketed actively as a major improvement in endovascular treatment. The idea of a filter catching any debris dislodged from the site of stenosis by balloon inflation or stent placement may be appealing but it must not be forgotten that they require passing of the stenosis in the first place and thus pose a potential risk of embolism to the distal vasculature. Filter devices may catch larger debris but may also lead to the splitting of soft material into many small parts that may pass through the filter mesh and cause multiple areas of ischaemic damage in the brain. It was the hope that the review might shed some light on the usefulness of cerebral filter devices but only two trials included data on the use of these devices in their publications. Their use was not allocated randomly and selection bias might have been operating. No conclusions should therefore be drawn from this subgroup analysis, which did not favour one method over the other.

Only two trials investigated endovascular treatment compared to surgery in asymptomatic patients. The numbers of patients and observed events were rather small and no conclusion can be drawn from this analysis. One further trial included larger numbers of asymptomatic patients but failed to report these results separately making it impossible to separate symptomatic from asymptomatic patients. The same was true for the comparison of endovascular treatment and medical therapy alone. Only two trials were identified and included in the review but both contained very small numbers of patients.

There are several reasons that would explain any underlying heterogeneity among trials. The endovascular technique used by the trials evolved over time. While CAVATAS started as a trial of balloon angioplasty, it allowed stenting as it became more widely available. The later trials exclusively used primary stenting as endovascular technique of choice. Devices available early on in the development of stenting have either undergone changes or are no longer available. This is a disadvantageous position for endovascular treatment, which has to compete with a technique that was able to evolve for many years relatively un-scrutinised before being tested and compared in the large clinical trials.

Heterogeneity may also stem from differences in baseline patient characteristics. Not all trials strictly recruited symptomatic patients only. In CAVATAS 12% asymptomatic patients were recruited in the endovascular treatment and 9% in the endarterectomy arm. The proportion of asymptomatic patients in SAPPHIRE was even larger with 68% of patients in the stenting group and 71% of patients in the surgery group being asymptomatic, making this effectively a trial in asymptomatic carotid stenosis. Moreover, patients were selected specifically with a high surgical risk. Given that those patients were thought to be at high risk of surgery, it may come as a surprise that SAPPHIRE reported an event rate of stroke or death within 30 days after the procedure plus ipsilateral stroke or death between 31 days and 1 year after treatment of 'only' 8.4%. However, as pointed out above, the majority of the patients in SAPPHIRE were asymptomatic and therefore, if they had had medical treatment, one would have expected an event rate of no more than 4%. Hence, 8.4% is a high event rate and in fact indicates that the patient should never have had revascularisation either by surgery or carotid stenting. CAVATAS did not specifically aim at recruiting high-risk patients but baseline patient characteristics suggest that patients in CAVATAS selected a higher proportion of patients at high surgical risk compared to NASCET or ECST. But what constitutes a high-risk patient remains poorly defined.

Baseline carotid stenosis also differed between the trials, which may account for differences in outcome and heterogeneity among trials. The surgical trials NASCET and ECST have shown that the risk of stroke is not independent of the degree of carotid stenosis.

Completed and stopped trials were included in this review, which may provide another source of heterogeneity among trials. Three of the included studies were terminated prematurely because of concerns over the safety of stenting. The Wallstent trial was stopped after a total of 210 patients had been enrolled. The primary endpoint of cumulative occurrence of ipsilateral stroke, procedure-related death or vascular death within one year was reported in 12.1% of patients in the stenting group and 3.6% of

patients in the endarterectomy group ( $p = 0.02$ ). The 30-day rate of death or stroke was 12.1% after stenting and 4.4% after endarterectomy ( $p = 0.049$ ). Based on this data and a futility analysis the study sponsor rather than the Data Safety and Monitoring Board intervened and stopped the trial. This was very controversial because the study sponsor took the decision despite of outcome events not having been validated in all patients and because there were concerns regarding the competence and experience of those undertaking stenting. No further publication has come forth since the presentation at the meeting of the American Stroke Association and it was not possible to further assess the trial.

The Leicester study was stopped after referral to the Data Monitoring Committee who invoked the stopping rule after only 17 patients had received the allocated treatment. Five of seven patients undergoing endovascular treatment suffered a stroke compared to ten uncomplicated carotid endarterectomies ( $p = 0.003$ ). The investigators felt that the trial could not be restarted even in an amended form because of difficulties with informed consent.

EVA-3S was stopped early following a pre-planned interim analysis after 527 patients had been randomised showed a significantly higher risk of 30-day stroke or death in the stenting arm compared to surgery (9.6% *vs.* 3.9%).

Evidence for long-term efficacy was very limited by only short periods of available follow up. Similar safety and potential advantages of endovascular treatment seem to justify carrying on with the randomised trials already underway. They will provide large numbers of patients that will help to resolve uncertainties.

The analyses of endovascular treatment versus endarterectomy in asymptomatic patients and endovascular treatment versus medical care in patients not suitable for surgery were based on very small numbers of patients and it would not be justified to form conclusions based on these findings.

The results of this Cochrane Review did not support a change in clinical practice away from carotid endarterectomy as the treatment of choice and strongly supported continuation of the ongoing trials.

## 11 The International Carotid Stenting Study

### 11.1 Rationale for ICSS

As demonstrated in the previous chapter, the Cochrane Systematic Review did not conclusively favour endovascular treatment over carotid endarterectomy (or vice versa) but strongly supported the continued randomisation of patients into the ongoing clinical trials. One of these trials concerned was the International Carotid Stenting Study (ICSS).

While CAVATAS showed similar outcomes after endovascular treatment compared to surgery, it was acknowledged that both techniques did carry a significant risk of causing a stroke (Brown *et al.* 2001). Technology particularly in the field of endovascular treatment had moved on since CAVATAS was conducted and the use of stents in addition or in place of balloon angioplasty became standard practice in endovascular management of carotid stenosis. Moreover, CAVATAS did not include enough patients (or observed sufficient numbers of outcome events) to show a statistically significant difference between treatments.

Encouraged by the findings of CAVATAS and taking into account the shortcomings of CAVATAS and changes in technology, ICSS was set up with the aim of investigating the risks and benefits of primary carotid stenting compared to surgery in what would eventually become the largest trial of carotid stenting in symptomatic stenosis to date.

### 11.2 Methods and Patients

#### 11.2.1 Trial Centres

ICSS is an international collaboration of 50 centres in Europe, Canada, Australia and New Zealand. The collaborating centres are listed in the Appendix. The trial was designed to compare the safety and long-term efficacy of carotid stenting and endarterectomy. The trial was approved by the Northwest Multicentre Research Ethics Committee in the UK.

Participating centres had the obligation to obtain site-specific approval from their local ethics committees.

Each centre wishing to participate in ICSS had to have a team in place consisting of at least a neurologist or physician with a special interest in stroke to see patients before randomisation and for follow-up, a designated surgeon with experience in carotid endarterectomy and a designated interventionist with expertise in carrying out angiography, angioplasty, and stenting. Centres were required to hold regular multidisciplinary meetings between the investigators to discuss management of patients with carotid artery stenosis. Investigators submitted their curricula vitae and audit data that documented satisfactory training and results of carotid treatment to the credential committee.

Centres were either enrolled as experienced or supervised centres, depending on the experience of the personnel carrying out the carotid surgery or intervention. Centres qualified as experienced if the surgeon had performed at least 50 carotid surgeries with a rate of ten cases per year and if the interventionist had performed a minimum of 50 stenting procedures with at least ten cases in the carotid artery. Centres not fulfilling either of these criteria were able to join as supervised centre and the trial procedures at these centres were proctored by an outside surgeon or interventionist who was appointed by the Trial Steering Committee to ensure that the centres became proficient in carrying out the procedure.

After completion of 20 cases with results deemed acceptable by the proctor and the credential committee centres were promoted to 'experienced' status. All patients enrolled in a centre after it was promoted were identified as such while patients enrolled prior to the centre's promotion were identified as 'supervised'. This was done to allow for investigating the influence of experience on outcome. While theoretically this policy applied to surgery and stenting, all centres classified as 'supervised' in ICSS were so because of a lack of experience in carotid stenting.

An independent Data Monitoring Committee that met on a regular basis monitored trial safety and advised the Trial Steering Committee.

### 11.2.2 Patients

Patients over the age of 40 years with symptomatic atheromatous disease of the extracranial internal carotid artery or at the level of the carotid bifurcation resulting in a stenosis measuring more than 50% using the NASCET criteria (Barnett *et al.* 1998) or non-invasive equivalent were eligible to join the trial. The multi-disciplinary team had to deem patients suitable for both surgery and stenting and in need of invasive treatment. No upper age limit was set by the protocol. Patients should only be randomised if the local investigators were uncertain which of the two treatments was best for the particular patient at the time.

The trial protocol specified that symptoms had to have occurred within 12 months prior to randomisation although it was recommended that the time between symptoms and randomisation should be less than six months. Patients had to be clinically stable and willing to have either treatment and participate in follow-up.

Patients unwilling or unable to provide written informed consent were excluded from the trial, as were patients who had a major stroke with no useful recovery of function within the territory of the treatable artery. Patients with stenosis that was known to be unsuitable for stenting (tortuous anatomy, visible thrombus present, proximal common carotid artery stenosis, pseudo-occlusion) or surgery (high stenosis, rigid neck) were excluded from participating in ICSS. Previous endarterectomy or stenting in the treatable artery, planned common carotid surgery, planned coronary artery bypass grafting or other major surgery within one month of carotid surgery or stenting also excluded patients from participation in the trial, as did a limited life expectancy (less than two years) due to a pre-existing condition.



### 11.2.3 Investigations Prior to Randomisation

Several investigations were required before entry into the study. They included routine haematology (full blood count, platelets), blood biochemistry (renal function, blood sugar, cholesterol), chest x-ray, and ECG. A brain scan (CT or MRI) was required to rule out any other pathology and to identify existing infarcts. It also served as baseline reference in case of subsequent cerebral infarction or haemorrhage.

The severity of carotid artery stenosis in the vessel to be treated had to be established and the contralateral carotid artery had to be assessed prior to randomisation. Several modalities were acceptable:

- Arch arteriogram showing both carotid bifurcations
- Selective catheter angiogram showing the carotid artery targeted for treatment AND non-invasive investigation of the contralateral carotid bifurcation
- Bilateral MR or CT carotid angiogram AND concordant ultrasound investigation.

Bilateral duplex and Doppler ultrasound alone was acceptable if it was standard practice at the centre to treat patients on the basis of ultrasound alone and the centre was able to provide proof of their ultrasound imaging's reliability through a clinical audit. It was recommended that patients allocated to stenting on the basis of non-invasive imaging and in whom subsequent angiography as part of the stenting procedure revealed one or more exclusion criteria crossed over to surgery or medical care as appropriate. Follow-up of these patients continued and they were included in the intention-to-treat analysis. A similar approach was recommended for patients allocated to surgery.

Baseline data including patient demographic data, blood results, existing medical risk factors, disability assessed with the modified Rankin scale (see appendix) and pre-randomisation imaging films or reports were reported to the Central Trial Office.

#### **11.2.4 Randomisation**

Eligible patients were randomised in 1:1 ratio to receive carotid artery stenting or carotid endarterectomy by telephone call to a computerised service provided by the Oxford Clinical Trials Service Unit whose staff had no further role in the trial. The allocated treatment was communicated to the local research team by either telephone or fax. Randomisation was stratified by centre with minimisation of sex, age, contralateral occlusion, and side of randomised artery. Minimisation was conducted separately for each centre and balanced between the two arms of the study. Patients in whom both carotid arteries needed treatment were randomised for the carotid artery to be treated first. Investigators were kept masked about the randomisation program to prevent them anticipating the next assignment. Patients and individuals delivering the treatment were not masked to treatment assignment. Apart from the trial statistician and the data monitoring committee, all investigators including the chief investigator remained masked to the results of the trial until recruitment was completed.

#### **11.2.5 Treatment**

##### **Surgery**

Carotid endarterectomy was carried out as soon after randomisation as possible by a designated surgeon. The protocol did not prescribe a specific surgical technique and individual centres were allowed to use whichever technique was their standard procedure including the use of local or general anaesthesia, shunts or patches, and standard or eversion endarterectomy.

##### **Stenting**

The protocol prescribed that carotid stenting should be carried out as soon as possible after randomisation using a percutaneous transluminal interventional technique from the femoral, brachial or common carotid artery by a designated interventional consultant and using an appropriate stent. Cerebral protection devices were recommended when the operator thought they could be safely deployed. Stents and other devices used for

carotid stenting were chosen at the discretion of the interventionist but had to be CE marked.

The combination of clopidogrel and aspirin was recommended to cover the period of stenting and for at least four weeks after the procedure. Heparin was mandatory during the procedure and discretionary thereafter.

Stenting and carotid endarterectomy were considered to have been initiated once anaesthesia (general or local) in preparation of the procedure was administered even if the procedure was subsequently abandoned before stent deployment or endarterectomy.

### **Medical Treatment**

The study protocol refrained from prescribing a specific medical treatment regimen. All patients were expected to receive 'best medical care' including antiplatelet therapy or anticoagulation and control of medical risk factors (hypertension, hyperlipidaemia, smoking) before treatment and throughout follow-up.

#### **11.2.6 Follow-up**

Patients were followed up by a neurologist or physician with a special interest in stroke medicine at each participating centre 30 days after treatment, six months after randomisation and annually thereafter. Carotid ultrasound using the methods explained in the earlier chapters of this thesis was carried out 30 days after treatment and yearly after randomisation to assess the patency of the treated carotid artery.

Neurological status, complications, and results of ultrasound investigations were reported in detail to the Central Trial Office. Two investigators reviewed the submitted data and requested further information as appropriate from the individual centres. One of two independent adjudicators further adjudicated all outcome events. Remaining differences were resolved by agreement.

### 11.2.7 Definitions of Outcome Events

Stroke was defined as an acute disturbance of focal neurological function with symptoms lasting more than 24 hours resulting from intracranial vascular disturbance. Visual loss resulting from embolic or haemodynamic retinal ischaemia lasting longer than 24 hours was included in this category. Events leading to a modified Rankin score of 3 or greater for longer than 30 days after onset were classified as disabling and the remaining events were classified as non-disabling. Events leading to death within 30 days after onset were classified as fatal.

An acute disturbance of focal neurological function with symptoms lasting less than 24 hours attributed to cerebrovascular disease defined a transient ischaemic attack (TIA). This category included acute total or partial loss of vision in one eye with recovery within 24 hours attributed to vascular disease (amaurosis fugax).

Cranial nerve palsies were defined as weakness or sensory impairment in the distribution of one of the cranial nerves attributed to the treatment. The degree of disability caused by cranial nerve palsies was assessed using the modified Rankin score.

Haematoma was defined as bleeding attributed to the treatment of carotid narrowing requiring evacuation, blood transfusion or prolonged hospital stay.

Myocardial infarction (MI) was defined by the presence of two out of three of the following criteria:

- Specific cardiac enzymes more than twice the upper limit of normal
- A history of chest discomfort for at least half an hour
- The development of specific abnormalities on a standard 12-lead ECG (e.g. Q waves)

### 11.2.8 Outcome Measures

The primary analysis specified in the protocol was the difference between groups in long-term rate of fatal or disabling stroke in any territory. Long-term was defined as 3 years and therefore data are not yet available for the analysis discussed here. The first secondary analysis specified in the protocol is discussed in this chapter: The differences in mortality and morbidity between groups within 30 days of carotid treatment. The main endpoint for the analysis of short-term safety data was defined prior to the analysis as:

- Any stroke or death or procedural myocardial infarction (MI)

Several additional secondary endpoints were also defined prior to the analysis of data:

- Any stroke
- Any stroke or death
- Any stroke or procedural death
- Disabling stroke or death (including fatal stroke)
- All cause death

Events relating to the various components of the primary endpoint, cranial nerve palsies, haematomas and Rankin score 30 days after treatment were also analysed.

Several pre-defined subgroup analyses were carried out. They were exploratory in nature and investigated the influence of various baseline characteristics on outcome.

### 11.2.9 Statistical Methods

A large difference in outcomes between the stenting and endarterectomy groups was not expected and the sample size was calculated to provide a reasonable estimate of the treatment effect. A sample size of 1500 patients from experienced centres was chosen on the basis that this would allow a 95% confidence interval to be measured with a width of

$\pm 3.3\%$  for the difference in risk of disabling stroke or death between treatment groups, based on an average of 12.5% of patients having the outcome. It was also calculated that this sample size would allow a 95% CI to be measured with a width of  $\pm 3.0\%$  for the secondary short-term outcome of 30-day stroke, death, or procedural MI, on the basis of an average of 10% of patients having the outcome.

Because some patients did not receive their allocated treatment and the timing of treatment after randomisation varied, two main analyses of short-term safety data were carried out.

A 120-day intention-to treat (ITT) analysis included all randomised patients and compared those allocated to endarterectomy to those allocated to stenting irrespective of whether they actually received the allocated treatment. An arbitrary cut-off point 120 days post randomisation was pre-defined for event-free patients. Patients with less than 120 days of follow-up were censored on the date of last known status. Censoring was assumed to be non-informative, i.e. a censored patient was assumed to have the same risk of an outcome event as those who had complete 120-day follow-up. Kaplan-Meier methods were used to estimate 120-day probabilities of an outcome event and subsequently the absolute difference between the two treatment groups and corresponding 95% confidence intervals. Cox proportional hazard methods were used to calculate the relative difference between treatment groups (hazard ratio) and corresponding 95% confidence intervals. Carotid endarterectomy was the reference group. Log rank tests were used to compare the survival curves. All events between randomisation up to 120 days thereafter were included in the analyses whether procedural or not. This analysis thus compared the policy of carotid stenting with endarterectomy on the short-term post-randomisation risk of an event.

The second analysis was a 30-day per-protocol analysis and evaluated the procedural risk. It included only those patients who received their allocated treatment. Patients who crossed over to an alternative treatment were excluded from the analysis. Only

events occurring after treatment and up to 30 days thereafter (procedural events) were included. Binominal regression methods were used to estimate the 30-day absolute risk difference and relative risk ratios and corresponding 95% confidence intervals. Chi-squared ( $\chi^2$ ) tests were used to test for differences between the two treatment groups. Only the first initiated ipsilateral treatment was considered but this could occur at any time after randomisation. A small number of procedures took place more than 120 days after randomisation.

Several pre-defined exploratory subgroup analyses were carried out to investigate whether the relative treatment effect for the 120-day intention-to-treat composite outcome of stroke, death, or procedural MI differed across various patient risk factor groups. Interaction tests were performed using Cox proportional hazard models. The subgroup analyses were based on the primary outcome measure. Stata release 11 was used for all analysis except the meta-analysis, which was done with ReviewManager version 5.

## **11.3 Results**

### **11.3.1 Baseline Characteristics**

Between 21<sup>st</sup> May 2001 and 20<sup>th</sup> October 2008, 1713 patients from 50 academic centres (see Appendix for list of participating centres) were randomly assigned to either carotid stenting (n = 855 patients) or carotid endarterectomy (n = 858). Three patients withdrew consent immediately after randomisation and were excluded from any further analysis. The remaining 1710 patients (stenting n = 853, surgery n = 857) were included in the analysis (Figure 11.1). 751 (88%) of patients assigned to stenting and 760 (89%) of patients assigned to endarterectomy were randomised at centres classified as experienced. Monitoring of adverse events led to concern about the stenting results of two investigators at supervised centres. These investigators were stopped from treating further patients within the trial and their centres were suspended from randomisation. All the patients at these centres allocated to stenting (n = 11, five with disabling stroke or

death) or endarterectomy during the same time period (n = 9, one with fatal stroke) were included in the analyses. One of the two centres subsequently restarted randomisation with a different investigator performing stenting.

The degree of stenosis in the randomised carotid artery exceeded 70% in the vast majority of patients. Contralateral stenosis greater than 50% was found in about one-third of the patients in both groups. Baseline patient characteristics were well balanced between the groups (Table 11.1).

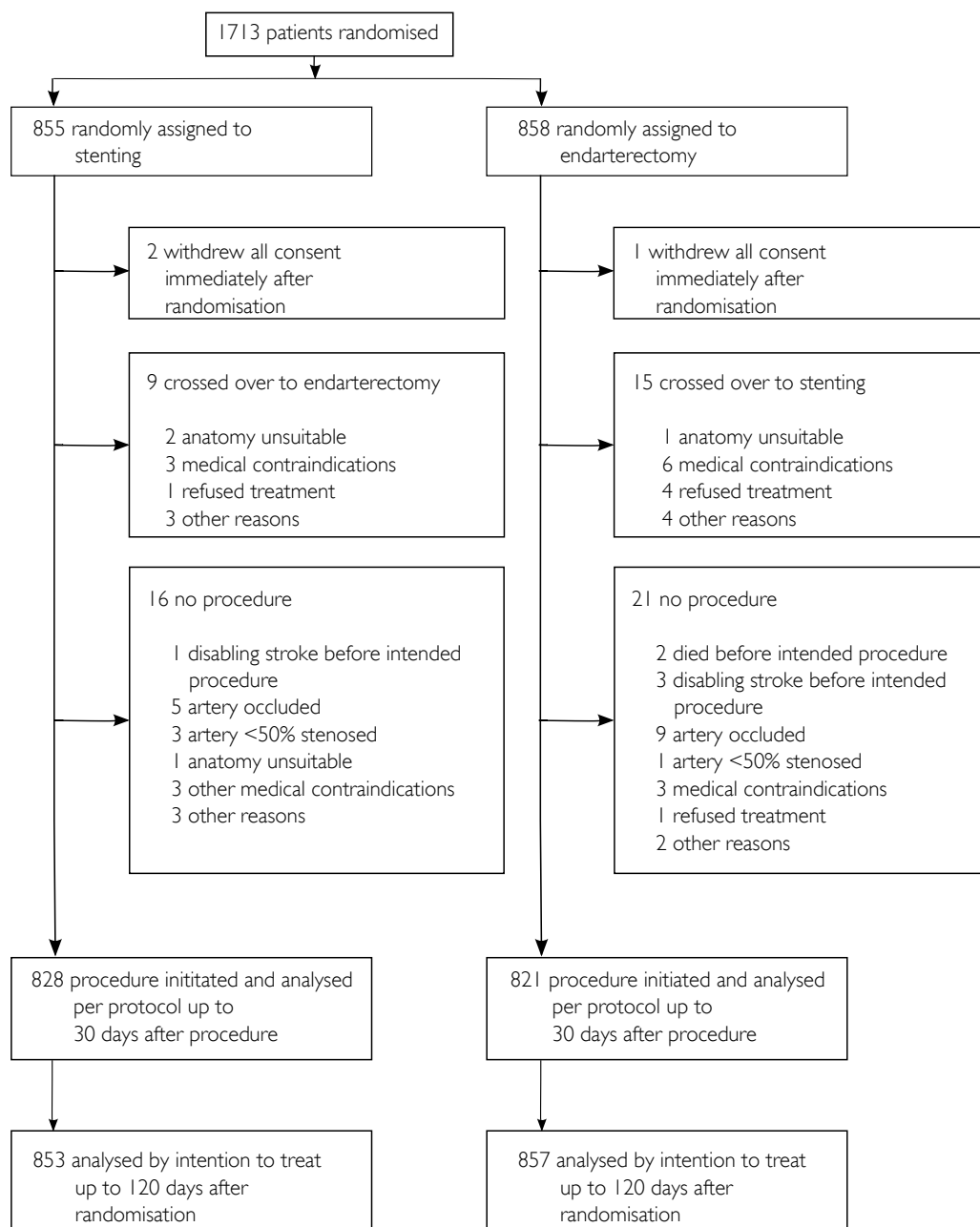
### 11.3.2 Delay to treatment

Patients allocated to carotid stenting received the allocated treatment with significantly shorter delay after randomisation than patients allocated to and receiving surgery (median 9 versus 11 days,  $p < 0.001$ ). While 70% of patients in the stenting group had to wait less than 14 days for treatment, only 57% patients received carotid endarterectomy within 14 days after randomisation (Figure 11.2).

The delay between the most recent event and treatment was also significantly shorter for patients allocated to carotid stenting: The median delay was 35 days for carotid stenting and 40 days for carotid endarterectomy ( $p = 0.013$ ). While 25% of patients were receiving their allocated stent within 14 days after the most recent event, only 18% of patients allocated to surgery were treated within this timeframe.



Figure 11.1 – ICSS: Trial profile



**Table 11.1 – ICSS: Patient characteristics at baseline per allocated treatment**

Data are number of patients (%) or mean (SD). CEA, carotid endarterectomy; SD, standard deviation; CABG, coronary artery bypass graft. \*Degree of stenosis measured by NASCET method at randomising centre. †If two events were reported on the same day, the more serious of the two was counted (stroke>retinal infarct>TIA>A fugax). ‡Some Rankin scores  $\geq 3$  were due to non-stroke disability (table continued on next page).

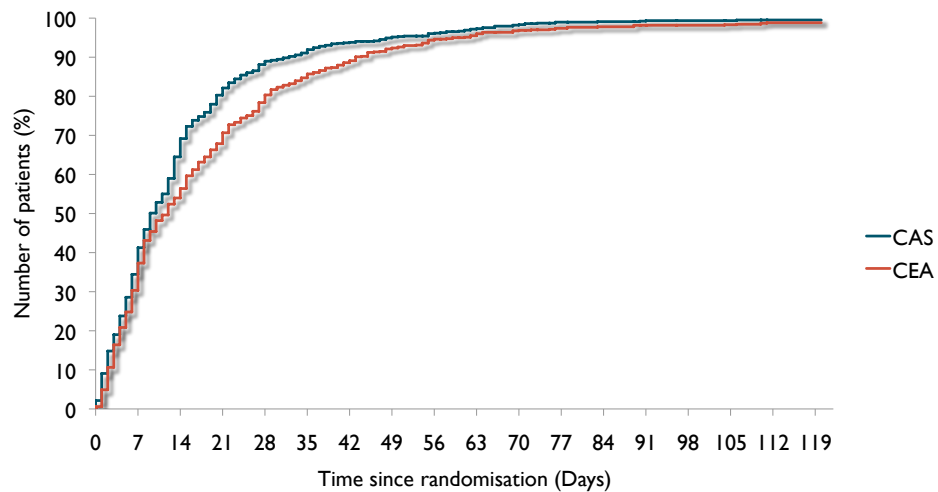
|  | Stenting<br>(n = 853) | CEA<br>(n = 857) |
|--|-----------------------|------------------|
| <b>Randomised at experienced centre</b>        | 751 (88%)             | 760 (89%)        |
| <b>Age (mean [SD], years)</b>                  | 70 [9]                | 70 [9]           |
| <b>Sex</b>                                     |                       |                  |
| Women  | 252 (30%)             | 251 (29%)        |
| Men  | 601 (70%)             | 606 (71%)        |
| <b>Vascular risk factors</b>                   |                       |                  |
| Hypertension                                   | 587 (69%)             | 595 (69%)        |
| Systolic blood pressure (mean [SD], mmHg)      | 147 [24]              | 146 [24]         |
| Diastolic blood pressure (mean [SD], mmHg)     | 79 [12]               | 78 [13]          |
| Diabetes mellitus                              | 184 (22%)             | 187 (22%)        |
| Treated hyperlipidaemia                        | 522 (61%)             | 562 (66%)        |
| Cholesterol (mean [SD], mmol/L)                | 4.8 [1.3]             | 4.9 [1.3]        |
| Current smoker                                 | 205 (24%)             | 198 (23%)        |
| Past smoker                                    | 408 (48%)             | 424 (49%)        |
| <b>Prior history of cardiovascular disease</b> |                       |                  |
| Myocardial infarction                          | 151 (18%)             | 156 (18%)        |
| Atrial fibrillation                            | 57 (7%)               | 59 (7%)          |
| Cardiac Failure                                | 23 (3%)               | 47 (5%)          |
| Angina in previous 6 months                    | 83 (10%)              | 77 (9%)          |
| Previous CABG                                  | 109 (13%)             | 116 (14%)        |
| Other cardio-embolic source                    | 19 (2%)               | 16 (2%)          |
| Peripheral artery disease                      | 139 (16%)             | 136 (16%)        |
| Degree of symptomatic carotid stenosis*        |                       |                  |

|   | Stenting<br>(n = 853) | CEA<br>(n = 857) |
|---|-----------------------|------------------|
| 50-69%  | 92 (11%)              | 76 (9%)          |
| 70-99%  | 761 (89%)             | 781 (91%)        |
| Degree of contralateral stenosis*                         |                       |                  |
| <50%  | 565 (66%)             | 561 (65%)        |
| 50-69%  | 128 (15%)             | 142 (17%)        |
| 70-99%  | 105 (12%)             | 110 (13%)        |
| Occluded  | 49 (6%)               | 37 (4%)          |
| Unknown   | 6 (1%)                | 7 (1%)           |
| Most recent ipsilateral event†                            |                       |                  |
| Amaurosis fugax   | 148 (17%)             | 142 (17%)        |
| Transient ischaemic attack                                | 273 (32%)             | 303 (35%)        |
| Ischaemic hemispheric stroke                              | 393 (46%)             | 376 (44%)        |
| Retinal infarct   | 26 (3%)               | 23 (3%)          |
| Unknown   | 13 (2%)               | 13 (2%)          |
| Event <6 months before randomisation                      | 826 (97%)             | 816 (95%)        |
| Event 6-12 months before randomisation                    | 27 (3%)               | 36 (4%)          |
| Multiple ipsilateral symptoms prior to randomisation      | 330 (39%)             | 317 (37%)        |
| Ipsilateral stroke prior to most recent ipsilateral event | 131 (15%)             | 106 (12%)        |
| Modified Rankin Score at Randomisation                    |                       |                  |
| 0-2   | 756 (89%)             | 744 (87%)        |
| 3-5‡  | 81 (10%)              | 99 (12%)         |
| Unknown   | 16 (2%)               | 14 (2%)          |

Table 11.1 continued

**Figure 11.2 – ICSS: Delay between randomisation and treatment**

Cumulative number of patients in whom allocated treatment was initiated per protocol plotted as a proportion (%) of the total number randomised in each treatment group (vertical axis), against the delay in days between the dates of randomisation and treatment (horizontal axis). CAS, carotid artery stenting; CEA, carotid endarterectomy.



### 11.3.3 Compliance with Allocated Treatment

Most patients had the treatment initiated that they were allocated. In the stenting group, nine patients crossed to surgery, of whom one patient refused stenting. A further 16 crossed to medical therapy. Of these, one patient had suffered a stroke prior to treatment and five patients were found to have an occluded carotid artery. This left 828 patients in the stenting group for the per-protocol analysis.

Of these 828 patients, 64 (8%) had their procedure aborted before the insertion of a stent (38 procedures were aborted because of difficulty gaining access to the stenosis, 15 were aborted because of the finding of an occluded artery, one patient had a fatal stroke, one patient had a fatal MI before completion of treatment, two had other medical complications, and further investigation in seven patients showed the artery to be < 50% stenosed). Of the 62 patients whose stenting procedure was aborted after initiation and who did not have a fatal event, 37 went on to have an ipsilateral endarterectomy, whereas 25 patients continued on medical therapy alone.

In the surgery group, 15 patients crossed to stenting. Of these, three patients refused surgery and in one patient it was impossible to gain access to the stenosis. An additional 21 patients crossed to medical therapy. Of these patients, one died before treatment, two suffered a disabling stroke before treatment, nine had an occluded carotid artery, and one patient refused invasive treatment. The remaining 821 patients were included in the per-protocol analysis.

Only 2 of the 821 patients whose allocated endarterectomy was initiated had their procedure aborted (one patient had an allergic reaction during general anaesthesia, the other became distressed and the endarterectomy had to be abandoned). Both patients had subsequent ipsilateral stenting.

#### **11.3.4 Intention-to-treat Analysis**

##### **Main Outcome Measure**

Stroke, Death or Procedural Myocardial Infarction

The main outcome of stroke, death or procedural MI was recorded in 72 patients allocated to carotid stenting and 43 patients allocated to carotid endarterectomy (Table 11.2).

The 120-day risk of stroke, death or procedural MI in patients allocated to carotid stenting was significantly higher than in the group of patients allocated to carotid endarterectomy (8.5% versus 5.2%, respectively). The absolute risk difference at 120 days was 3.3% (95% CI 0.9 to 5.7) and the hazard ratio was 1.69 (95% CI 1.16 to 2.45,  $p = 0.006$ ) in favour of carotid endarterectomy (Table 11.2 and Table 11.3).

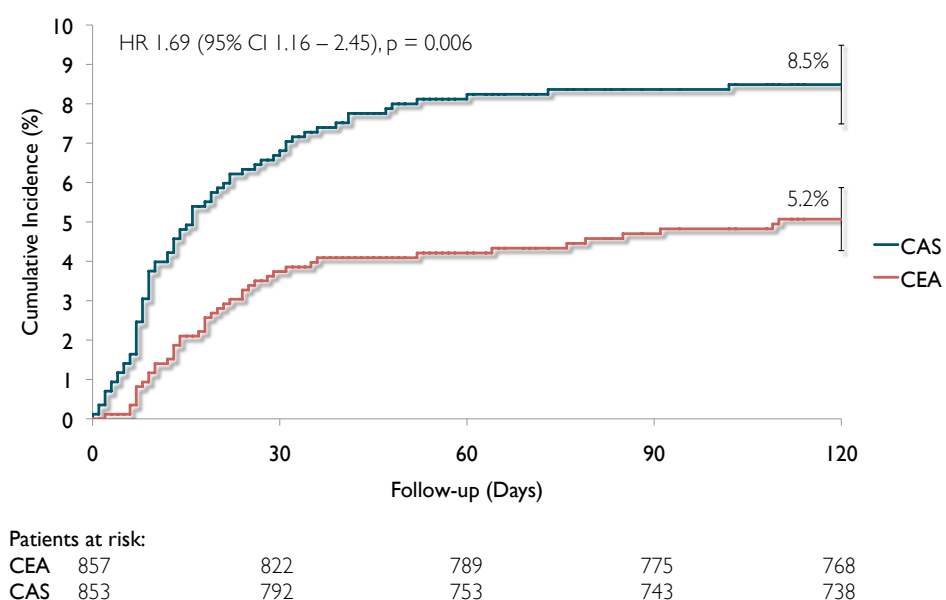
**Table 11.2 – ICSS: Main outcome measures (Intention-to-treat analysis)**

Data are number of first events (Kaplan-Meier estimate at 120 days), hazard ratios or risk differences (95% CI). Risk differences are calculated from Kaplan-Meier estimates at 120 days. CAS, carotid artery stenting; CEA, carotid endarterectomy; MI, myocardial infarction; HR, hazard ratio; RD, risk difference; CI, confidence interval. \*Log-rank test.

|                                | CAS<br>n = 853 | CEA<br>n = 857 | HR (95% CI)       | RD (95% CI)     | P-<br>value* |
|--------------------------------|----------------|----------------|-------------------|-----------------|--------------|
| Primary outcome                |                |                |                   |                 |              |
| Stroke, death or procedural MI | 72 (8.5%)      | 44 (5.2%)      | 1.69 (1.16, 2.45) | 3.3 (0.9, 5.7)  | 0.006        |
| Secondary outcomes             |                |                |                   |                 |              |
| Any stroke                     | 65 (7.7%)      | 35 (4.1%)      | 1.92 (1.27, 2.89) | 3.5 (1.3, 5.8)  | 0.002        |
| Any stroke or death            | 72 (8.5%)      | 40 (4.7%)      | 1.86 (1.26, 2.74) | 3.8 (1.4, 6.1)  | 0.001        |
| Any stroke or procedural death | 68 (8.0%)      | 36 (4.2%)      | 1.95 (1.30, 2.92) | 3.8 (1.5, 6.0)  | 0.001        |
| Disabling stroke or death      | 34 (4.0%)      | 27 (3.2%)      | 1.28 (0.77, 2.11) | 0.8 (-0.9, 2.6) | 0.34         |
| All cause death                | 19 (2.3%)      | 7 (0.8%)       | 2.76 (1.16, 6.56) | 1.4 (0.3, 2.6)  | 0.017        |

**Figure 11.3 – ICSS: 120-day cumulative incidence of stroke, death or procedural MI (ITT)**

Shown is the Kaplan-Meier curve for the primary outcome measure of stroke, death or procedural MI up to 120 days after randomisation in the intention-to-treat analysis. The vertical bars represent the standard errors of the estimated 120-day cumulative incidence. CAS, carotid stenting; CEA, carotid endarterectomy.

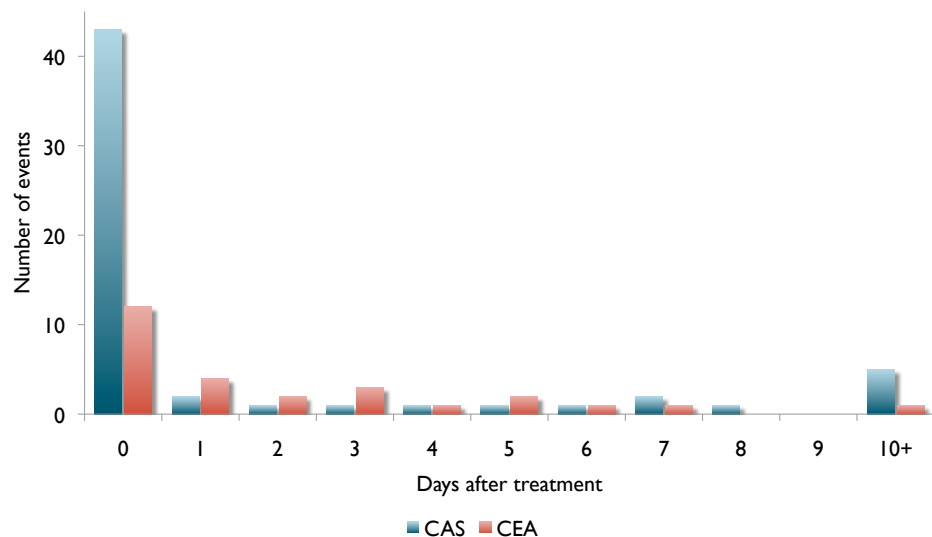


Most of the short-term outcome events occurred within 30 days of the first ipsilateral procedure. This was the case in 61 patients in the stenting group and 31 patients in the endarterectomy group (Figure 11.4). However, two events in the stenting group and one event in the surgery group occurred prior to the allocated treatment and six events in each group occurred more than 30 days after treatment but before the 120-day cut off. Three patients in the stenting group and six patients in the surgery group who had no attempted ipsilateral procedure experienced an event.

In 23 patients in the stenting arm and six patients in the surgery arm, the stroke occurring on the same day of the procedure was thought to be directly related to the procedure.

**Figure 11.4 – ICSS: Timing of first stroke after allocated procedure**

23 strokes in the stenting arm and 6 strokes in the surgery arm were directly related to the procedure and classified 'procedural'. Day 0 indicates the day of the procedure. CAS, carotid stenting; CEA, carotid endarterectomy.



## Additional Outcome Measures

### Stroke

Stroke was recorded in 65 patients (58 ipsilateral strokes) allocated to stenting and 35 patients (30 ipsilateral strokes) allocated to carotid endarterectomy (Table 11.2 and Table 11.3). The 120-day risk of stroke was 7.7% in patients allocated to stenting and 4.0% in patients allocated to surgery, a 3.6% (95% CI 1.4 to 5.9) absolute risk difference. The hazard ratio was 1.97 (95% CI 1.30 to 2.99,  $p = 0.001$ ) in favour of carotid endarterectomy.

In both groups the majority of strokes were non-disabling lasting more than 7 days. In the stenting group 39 strokes were non-disabling of which 31 lasted more than 7 days. Fourteen strokes in the surgery group were non-disabling of which nine lasted more than 7 days.

Fatal stroke occurred more frequently in the carotid stenting group ( $n = 9$ ) than in the surgery group ( $n = 2$ ). The number of disabling stroke was similar in both groups, with 17 disabling strokes in the stenting group and 20 disabling strokes in the surgery group.



**Table 11.3 – ICSS: Number of outcome events recorded between randomisation and 120 days in the intention-to-treat (ITT) analysis and between initiation of treatment and 30 days after treatment in the per-protocol analysis.**

Data are number of first events of each type. \*In 2 patients this was a retinal infarct. One patient had both an ischaemic and a haemorrhagic stroke. †1 patient had a subsequent fatal MI and 1 patient also had a non-disabling stroke that lasted for more than 7 days. ‡1 patient had a subsequent disabling stroke. ||2 patients subsequently died of non-stroke, non-MI cause. ¶The cranial nerve palsy in this patient allocated CAS, which was initiated but aborted, occurred after CEA carried out within 30 days of attempted but abandoned stent procedure. §One patient had a non-fatal myocardial infarction within 30 days of the first procedure, which was undertaken more than 120 days after randomisation. This MI was therefore excluded from the ITT analysis but was included in the per-protocol analysis. \*\*Severe haematoma was defined as one that required surgical evacuation or blood transfusion or resulted in prolonged hospital stay.

|                               | ITT analysis      |                         | Per-protocol analysis |                         |
|-------------------------------|-------------------|-------------------------|-----------------------|-------------------------|
|                               | Stenting<br>n=853 | Endarterectomy<br>n=857 | Stenting<br>n=828     | Endarterectomy<br>n=821 |
| Any stroke                    | 65*               | 35                      | 58*                   | 27                      |
| Ipsilateral stroke            | 58                | 30                      | 52                    | 25                      |
| Ischaemic stroke              | 63                | 28                      | 56                    | 21                      |
| Haemorrhagic stroke           | 3                 | 5                       | 2                     | 5                       |
| Uncertain pathology           | 0                 | 2                       | 0                     | 1                       |
| Non-disabling stroke          | 39                | 14                      | 36                    | 11                      |
| Lasting fewer than 7 days     | 9†                | 5‡                      | 8†                    | 5‡                      |
| Lasting more than 7 days      | 31                | 9                       | 29                    | 6                       |
| Disabling stroke              | 17                | 20                      | 14                    | 14                      |
| Fatal stroke                  | 9                 | 2                       | 8                     | 3                       |
| Procedural MI                 | 3                 | 4                       | 3                     | 5                       |
| Non-fatal MI                  | 0                 | 4                       | 0                     | 5§                      |
| Fatal MI                      | 3                 | 0                       | 3                     | 0                       |
| Non-stroke, Non-MI death      | 7                 | 5                       | 1                     | 1                       |
| Cranial nerve palsy           | 1¶                | 45                      | 1¶                    | 45                      |
| Disabling cranial nerve palsy | 1¶                | 1                       | 1¶                    | 1                       |
| Haematoma                     | 31                | 50                      | 30                    | 50                      |
| Severe haematoma**            | 9                 | 28                      | 8                     | 28                      |

#### Any Stroke or Death

The combined outcome of any stroke or death was also more frequent in the stenting group and was recorded in 72 patients allocated to this treatment and in 40 patients allocated to carotid endarterectomy. The 120-day risk was 8.5% for patients allocated to carotid stenting and 4.7% for patients allocated to surgery. The absolute risk difference was 3.8% (95% CI 1.4 to 6.1) and the hazard ratio was 1.86 (95% CI 1.26 to 2.74,  $p = 0.001$ ) in favour of carotid endarterectomy (Table 11.2 and Figure 11.6).

#### Stroke or Procedural Death

Disabling stroke or procedural death was recorded in 68 patients in the stenting group and 36 patients in the surgery group. The rate of any stroke or procedural death was significantly higher in the stenting group than in the carotid endarterectomy group (8.0% versus 4.2%, HR 1.95, 95% CI 1.30 to 2.92,  $p = 0.001$ , Table 11.2).

#### Disabling Stroke or Death

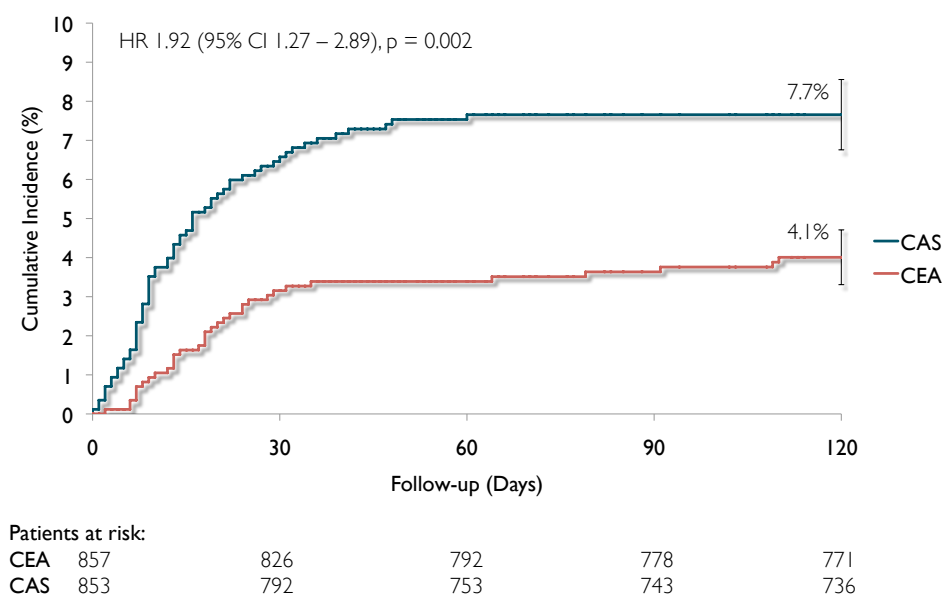
This combined outcome was recorded in 34 patients allocated to carotid stenting and 27 patients allocated to carotid endarterectomy. The 120-day risks in both arms were not significantly different (4.0% versus 3.2%, respectively). The hazard ratio did not significantly favour either treatment (HR 1.28, 95% CI 0.77 to 2.21,  $p = 0.34$ , Table 11.2 and Figure 11.7).

#### All Causes of Death

Nineteen patients allocated to stenting and 7 patients allocated to carotid endarterectomy died between randomisation and 120 days thereafter. The 120-day risk was estimated at 2.3% in the stenting group and 0.8% in the surgery group, a 1.4% (95% CI 0.3 to 2.6) absolute risk difference. The hazard ratio was 2.76 (95% CI 1.16 to 6.56,  $p = 0.0167$ ) in favour of carotid endarterectomy (Table 11.2 and Figure 11.8).

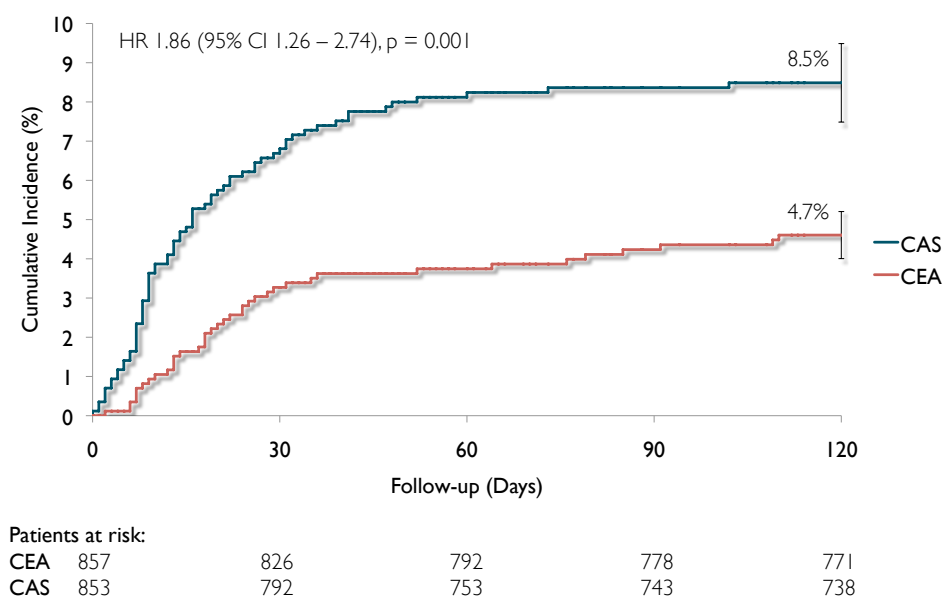
**Figure 11.5 – ICSS: 120-day cumulative incidence of any stroke (ITT)**

Shown is the Kaplan-Meier curve for the primary outcome measure of any stroke up to 120 days after randomisation in the intention-to-treat analysis. The vertical bars represent the standard errors of the estimated 120-day cumulative incidence. CAS, carotid stenting; CEA, carotid endarterectomy.



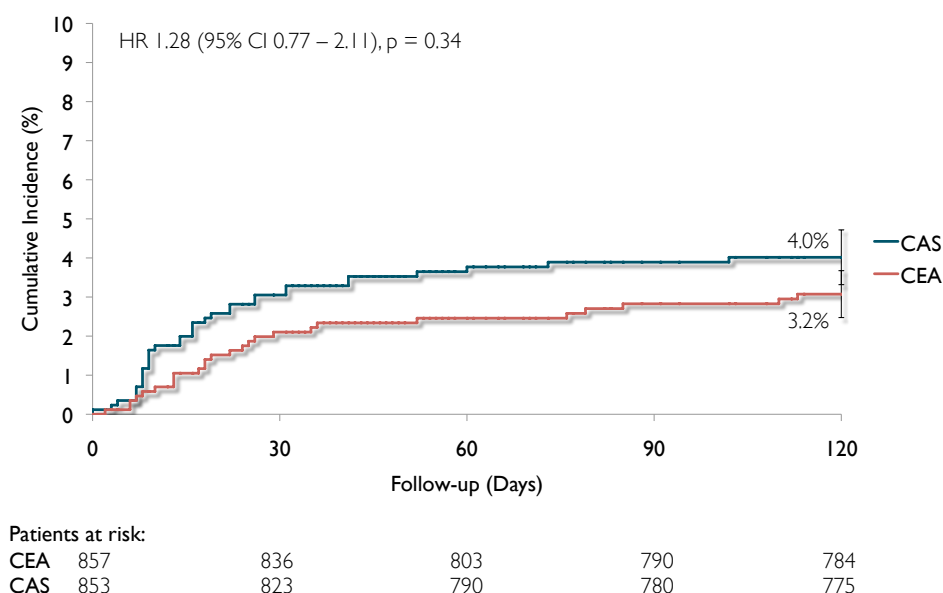
**Figure 11.6 – ICSS: 120-day cumulative incidence of stroke or death (ITT)**

Shown is the Kaplan-Meier curve for the primary outcome measure of stroke or death up to 120 days after randomisation in the intention-to-treat analysis. The vertical bars represent the standard errors of the estimated 120-day cumulative incidence. CAS, carotid stenting; CEA, carotid endarterectomy.



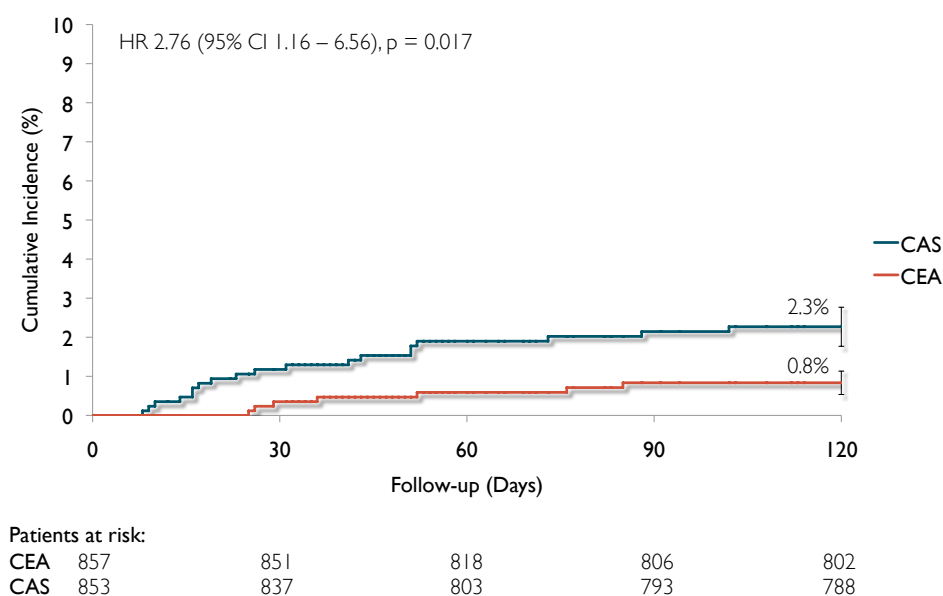
**Figure 11.7 – ICSS: 120-day cumulative incidence of disabling stroke or death (ITT)**

Shown is the Kaplan-Meier curve for the primary outcome measure of disabling stroke or death up to 120 days after randomisation in the intention-to-treat analysis. The vertical bars represent the standard errors of the estimated 120-day cumulative incidence. CAS, carotid stenting; CEA, carotid endarterectomy.



**Figure 11.8 – ICSS: Any cause of death 120-day cumulative incidence of any cause of death (ITT)**

Shown is the Kaplan-Meier curve for the primary outcome measure of any cause of death up to 120 days after randomisation in the intention-to-treat analysis. The vertical bars represent the standard errors of the estimated 120-day cumulative incidence. CAS, carotid stenting; CEA, carotid endarterectomy.



## Other Peri-procedural Complications

### Cranial Nerve Palsy

While 45 patients allocated to carotid endarterectomy suffered a cranial nerve palsy, this was also the case in one patient allocated to carotid stenting. However, this patient required carotid endarterectomy within 30 days after attempted carotid stenting and the cranial nerve palsy was a result of the surgery. Since it occurred within 30 days of stenting, it had to be counted against carotid stenting. This cranial nerve palsy and an additional one in the carotid surgery group was disabling, i.e. the patient required the placement of a percutaneous endogastric tube.

### Myocardial infarction

Procedural myocardial infarction was recorded in three patients allocated to carotid stenting and four patients allocated to carotid endarterectomy. All three MIs in the former group and none in the latter group were fatal.

### Haematoma

Haematoma was more frequently observed in patients allocated to carotid endarterectomy and was recorded in 50 patients in this treatment group, of which 28 required surgical evacuation, blood transfusion or resulted in a prolonged hospital stay (severe haematoma). In patients allocated to stenting, this outcome was recorded in only 31 cases, of which nine were classified severe.

## Subgroup Analyses

A number of pre-defined subgroup analyses were carried out based on the main short-term endpoint using the intention-to-treat dataset. The results are summarised in Figure 11.9.

The analyses carried out failed to identify a subgroup in which stenting was significantly favoured over surgery. Patients without treated hypertension (HR 3.25, 95% CI 1.46 to 7.20) derived a greater benefit from surgery than patients with treated hypertension (HR

1.29, 95% CI 0.83 to 2.00) and the interaction test showed a significant interaction between risk factor and treatment ( $p = 0.039$ ).

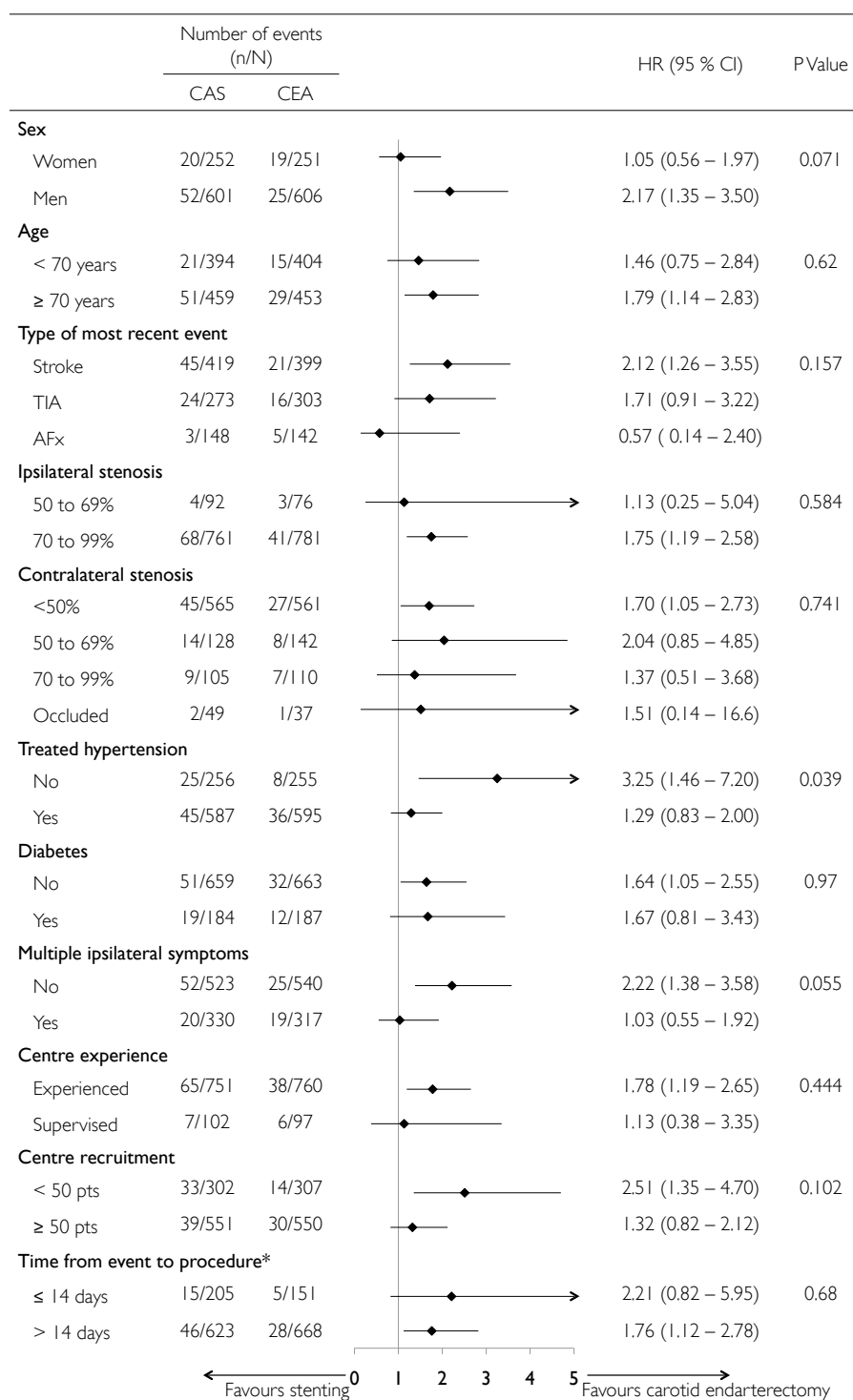
The benefit of surgery was also more pronounced in men (HR 2.17, 95% CI 1.35 to 3.50) compared to women (HR 1.05, 95% CI 0.56 to 1.97), but the treatment interaction test failed to reach statistical significance ( $p = 0.071$ ).

The recent frequency of ipsilateral symptoms appeared to influence the outcome. Patients with only a single event benefited from surgery to a greater extent than those patients with multiple events (HR 2.22, 95% CI 1.38 to 3.58 *versus* HR 1.03, 95% CI 0.55 to 1.92). But the treatment interaction test did not reach statistical significance ( $p = 0.055$ ).

There was no evidence that the relative increase in the hazard of an event in the stenting arm compared to the surgery arm differed significantly across the other subgroups, although there were trends towards the risk of stenting being less in patients under the age of 70, those with stenosis of 50 to 69% compared to 70 to 99%, patients presenting with amaurosis fugax and in centres recruiting more than 50 patients to the trial. There was no significant difference between the results in supervised centres and experienced centres (stenting risk 6.9% *versus* 8.7% respectively). There was also no difference in risks depending on whether patients were treated within 14 days of the index event or not.

**Figure 11.9 - ICSS: Subgroup analysis of the rates of the primary outcome measure**

Subgroups are defined according to baseline characteristics and analysed by intention to treat, \*with the exception of time from index event to treatment, which is analysed per-protocol. N, number of patients; n, number of events; HR, hazard ratio. P values are associated with treatment-covariate interaction tests. CAS, carotid artery stenting; CEA, carotid endarterectomy; TIA, transient ischaemic attack; AFx, amaurosis fugax



### 11.3.5 Per-protocol Analysis

Only events occurring within 30 days after the procedure were considered in this analysis.

#### Main Outcome Measure

Stroke, Death or Procedural Myocardial Infarction

The combined primary outcome measure was recorded in twice as many patients in whom the allocated carotid stenting procedure was initiated (n = 61) than in patients in the allocated surgery had been initiated (n = 31). The 30-day procedural risk was 7.4% after stenting and 4.0% after surgery. The absolute difference in risk was 3.3% (95% CI 1.1 to 5.6) and the hazard ratio significantly favoured carotid endarterectomy (HR 1.83, 95% CI 1.21 to 2.77, p = 0.0034, Table 11.4).

**Table 11.4 - ICSS: Main outcome measures between initiation of treatment and 30 days after treatment (Per-protocol analysis)**

Data are number of first events (%), risk ratios or risk differences (95% CI). See text for definition of per-protocol. CAS, carotid artery stenting; CEA, carotid endarterectomy; MI, myocardial infarction; RD, risk difference.

|                           | CAS<br>n = 828 | CEA<br>n = 821 | Risk ratio<br>(95% CI) | RD (95% CI)     | P-<br>value* |
|---------------------------|----------------|----------------|------------------------|-----------------|--------------|
| Primary outcome           |                |                |                        |                 |              |
| Stroke, death or MI       | 61 (7.4%)      | 33 (4.0%)      | 1.83 (1.21, 2.77)      | 3.3 (1.1, 5.6)  | 0.003        |
| Secondary outcomes        |                |                |                        |                 |              |
| Any stroke                | 58 (7.0%)      | 27 (3.3%)      | 2.13 (1.36, 3.33)      | 3.7 (1.6, 5.8)  | 0.001        |
| Any stroke or death       | 61 (7.4%)      | 28 (3.4%)      | 2.16 (1.40, 3.34)      | 4.0 (1.8, 6.1)  | 0.0004       |
| Disabling stroke or death | 26 (3.1%)      | 18 (2.2%)      | 1.43 (0.79, 2.59)      | 0.9 (-0.6, 2.5) | 0.23         |
| All cause death           | 11† (1.3%)     | 4 (0.5%)       | 2.73 (0.87, 8.53)      | 0.8 (-0.1, 1.8) | 0.072        |



## Additional Outcome Measures

### Stroke

Any stroke was recorded in 58 patients after the allocated stenting procedure was initiated and 27 patients after the allocated carotid endarterectomy was carried out. The 30-day procedural risk was 7.0% in the former group and 3.3% in the latter. The absolute risk difference was 3.7% (95% CI 1.6 to 5.8%) and the hazard ratio 2.13 (95% CI 1.36 to 3.33,  $p = 0.0006$ ) in favour of endarterectomy (Table 11.4).

Non-disabling stroke was the main contributor to this outcome, with 36 events in the stenting group and 11 events in the endarterectomy group falling into this category (Table 11.3).

Fatal stroke was more common after stenting. While eight patients suffered a fatal stroke after stenting, only one patient suffered a fatal stroke after the allocated carotid endarterectomy had been initiated.

Disabling stroke occurred 14 times within 30 days of the allocated procedure in both treatment groups.

### All Causes of Death

Eleven patients in the carotid stenting group and four patients in the surgery group died within 30 days after the allocated treatment had been attempted. The 30-day risk was estimated as 1.3% after stenting and 0.5% after surgery, equivalent to an absolute risk difference of 0.8% (95% CI -0.1 to 1.8). The hazard ratio was 2.73 (95% CI 0.87 to 8.53) and did not significantly favour either treatment ( $p = 0.0720$ , Table 11.4).

### Any Stroke or Death

Any stroke or death was recorded in 61 patients in the carotid stenting group and 28 patients in the surgery group. The 30-day risk of any stroke or death was 7.4% in the former treatment group and 3.4% in the latter group. The absolute risk difference was 4.0

(95% CI 1.8 to 6.1). The hazard ratio was 2.16 (95% CI 1.40 to 3.34,  $p = 0.0004$ ) and significantly favoured carotid endarterectomy (Table 11.4).

#### Disabling or Fatal Stroke or Non-stroke Death

This outcome was observed in 26 patients following carotid stenting and 18 patients after endarterectomy. The 30-day procedural risks were 3.1% and 2.2%, respectively, an absolute risk difference of 0.9% (95% CI -0.6 to 2.5). The hazard ratio was 1.43 (95% CI 0.79 to 2.59,  $p = 0.23$ ) and did not favour either treatment (Table 11.4).

#### Other Peri-procedural Complications

##### Cranial Nerve Palsy

The same distribution and number of cranial nerve palsies as in the intention-to-treat analysis were observed when using the criteria for the per-protocol analysis (44 cranial nerve palsies in the carotid endarterectomy group *versus* one in the stenting group). The cranial nerve palsy attributed to carotid stenting occurred in a patient, in whom carotid endarterectomy carried out shortly after unsuccessful stenting caused a cranial nerve palsy within 30 days of the originally attempted stenting procedure.

##### Myocardial infarction

The per-protocol analysis attributed five non-fatal and no fatal myocardial infarctions to the carotid surgery group. All three recorded myocardial infarctions in the stenting group were fatal.

##### Haematoma

Eight of 30 haematomas in the carotid stenting group required surgical evacuation, blood transfusion or prolonged hospital stay. The same was true for 28 out of 50 haematomas attributed to carotid surgery.

## 11.4 Discussion

The International Carotid Stenting Study is the largest randomised clinical trial of carotid stenting and endarterectomy to date and the first completed trial to show a significantly higher short-term risk of stroke, death or peri-procedural myocardial infarction in patients allocated stenting (3.3% absolute risk difference in favour of endarterectomy).

The excess of non-disabling stroke and a higher number of fatal strokes in patients allocated to carotid stenting were the main driving forces behind the difference in the 120-day risk between stenting (8.5%) and carotid endarterectomy (5.2%) in the main short-term outcome. The risk of death not related to stroke or myocardial infarction was similar in both groups as was the overall number of myocardial infarctions.

The results of the per-protocol analysis reinforce the findings of the intention-to-treat analysis. The fact that (with the exception of all-cause death) the per-protocol and intention-to-treat analyses provided similar results, suggest that the overall findings are reliable and robust. The difference between groups in the per-protocol analysis was mainly attributable to an excess of non-disabling stroke in the stenting group compared with the endarterectomy group, but there were also more fatal strokes and fatal myocardial infarctions in the stenting group. By contrast, the numbers of disabling strokes in the two groups were identical and the rate of disabling stroke or death was not significantly different between the groups.

All myocardial infarctions recorded in the stenting group were fatal while all myocardial infarctions in the surgery group were non-fatal. The overall number of heart attacks was small and not too much weight should be attached to this observation.

The distribution of stroke severity is interesting in that the number of disabling strokes exceeded the number of non-disabling strokes in the carotid endarterectomy group ( $n = 19$  *versus*  $n = 14$ ). No other randomised clinical trial of carotid stenting or surgery has found more disabling than non-disabling strokes in either the stenting or the surgery group. This may suggest that non-disabling strokes may have been missed in the surgery

group in ICSS. However, it may be a chance finding and should not distract from the overall result.

Investigators who undertook follow-up assessments were not masked to treatment allocation, leading to the possibility of ascertainment bias of minor events. A post-analysis audit has confirmed that all but 77 patients were seen for follow-up by a neurologist or stroke physician, or by research staff not directly involved in the revascularisation procedures. A sensitivity analysis excluded the 77 patients seen for follow-up by a surgeon only and provided similar results to those of the full analysis, making it unlikely that biased reporting affected the results. This is supported by the results of a blinded MRI sub analysis of ICSS (Bonati *et al.* 2010b). This sub analysis showed a significantly higher proportion of patients with new ischaemic lesions on MRI in the stenting group than in the endarterectomy group (50% *versus* 17%, adjusted odds ratio 5.21, 95% CI 2.78 – 9.79,  $p < 0.0001$ ). The most likely explanation for the excess risk of non-disabling stroke associated with stenting is that it is related to instrumentation of the carotid stenosis, given that most strokes occurred on the day of treatment.

ICSS confirmed previous findings that cranial nerve palsy and haematoma were both more common after carotid endarterectomy than after stenting. The cranial nerve palsy attributed to stenting in this trial in fact occurred following surgery. Timing of the surgery and occurrence of the nerve injury within 30 days after attempted stenting meant that the cranial nerve palsy had to be attributed to the stenting group. Two cranial nerve palsies were considered to be disabling and this should serve as a reminder that they are an important complication of carotid surgery. In almost 25% of patients, cranial nerve palsy was associated with haematoma. However, the long-term outcome of non-disabling stroke might be worse than that of non-disabling cranial nerve palsy. A recent symptomatic review has highlighted the increased risk of dementia associated with recurrent stroke (Pendlebury *et al.* 2009a). The long-term consequences of the non-disabling stroke in ICSS may only become evident with further follow-up, which will include measures of disability and quality of life.

Patients who received a stent had a shorter wait from the most recent stroke or TIA to treatment than did those who received endarterectomy. But even so only 25% of patients in the stenting group were treated within 14 days of symptoms, compared to 18% of those in the endarterectomy group. However, there was no difference in the risks of stenting compared with endarterectomy whether or not patients were treated within 14 days of symptoms or later. Several strokes occurred before treatment was initiated (five *versus* seven) and several patients developed asymptomatic carotid artery occlusion before treatment (five *versus* nine), emphasising the importance of treating carotid stenosis as soon as possible after symptoms.

The subgroup analyses were only exploratory in nature and will inform future analyses of combined data from the large trials. The overall message from these analyses is that so far no subgroup of patients substantially benefiting from stenting instead of surgery could be identified. It does suggest that carotid artery stenting may have a similar risk to endarterectomy in women, but that the intervention was more hazardous than endarterectomy in men. The difference, which did not reach statistical significance, seemed to be largely explained by a higher risk of outcome events associated with endarterectomy in women than in men. This finding is consistent with most large studies and was also seen in EVA-3S, in the pooled analysis of the major carotid endarterectomy trials, and in a systematic review of the published series (Rothwell *et al.* 2004b; Bond *et al.* 2005; Mas *et al.* 2008). Stenting seemed more hazardous, and endarterectomy less hazardous, in patients without treated hypertension at baseline than in patients with treated hypertension, but the reasons remain unclear. However, a systematic review of predictors of stroke and death caused by carotid endarterectomy showed a similar increase in risk of stroke or death associated with hypertension (HR 1.82, 95% CI 1.37 – 2.41,  $p < 0.0001$ ) in accordance with our findings (Rothwell *et al.* 1997). In patients whose most recent event was an episode of amaurosis fugax the risk of stenting was smaller than the risk of surgery. But interestingly, while the presence of a particular risk factor tended to increase the risk of carotid endarterectomy the same risk

factor tended to reduce the risk of stenting. The observation that a treatment should become 'safer' in patients who because of their risk factor profile are thought to be at increased risk of intervention is somewhat counter-intuitive. A possible explanation of this phenomenon may be that the inherent risk of stenting is much greater than the low risk of an outcome event in patients without risk factor than it is the case in patients with risk factor. It somewhat supports the notion of stenting being more suitable for 'high-risk' patients. But the effect is not as large as it may have been hoped and certainly not large enough to tip the scale in favour of stenting. This may change however, if individual patient data from the large trials are combined.

It should be pointed out, that the term 'high risk' is very poorly defined. Peter Rothwell pointed out in his comments on the long-term CAVATAS results that most patients who have undergone stenting for symptomatic carotid stenosis outside randomised trials would have met the inclusion criteria for the large trials (Rothwell 2009).

ICSS, SPACE and EVA-3S formed a trio of clinical trials comparing carotid stenting and carotid endarterectomy in patients with symptomatic carotid stenosis. They had very similar study protocols and were conducted at the same time. Neither SPACE nor EVA-3S reached their predefined sample size, albeit for different reasons (Mas *et al.* 2006; Ringleb *et al.* 2006). The publication of SPACE and EVA-3S in 2006 sparked intense debate. SPACE was very much in agreement with the Cochrane Review in not showing a significant difference between endovascular treatment and surgery, whereas EVA-3S was regarded as the "odd kid on the block". Much was made of the requirements for centres to join EVA-3S (Harjai *et al.* 2007; Naylor 2007; Qureshi 2007; Setacci *et al.* 2007; Beckett *et al.* 2008). It was attempted to explain the high complication rate of stenting (9.6%) with the level of experience required from stenting personnel. In hindsight, the focus should have been on the low complication rate following surgery.

The findings of ICSS now vindicate EVA-3S. The absolute risk difference between stenting and surgery for stroke, death, or procedural MI in ICSS is very similar although

smaller than that in EVA-3S (3.3% and 5.7%). Both ICSS and EVA-3S stand out from other trials of stenting *versus* surgery with a comparably low complication rate following surgery (3.9% and 5.1%), which is approximately half that reported in ECST and CAVATAS (Farrell *et al.* 1998; Brown *et al.* 2001). ICSS and EVA-3S are therefore more a testament to the safety improvements achieved in carotid endarterectomy over the years rather than a failure of carotid stenting as such.

It is unclear why the often-evoked “improvements in stenting technology” such as the introduction of cerebral filter devices and a wealth of different stenting systems have thus far have not led to a clear improvement in outcome. It could even be argued that rather than improving the safety of the procedure over the years the technological changes have done more harm than good. This argument is supported by the lower complication rate following stenting in SPACE compared to EVA-3S and ICSS. Roughly 20% of patients in SPACE were treated with a protection device. The use of protection devices was mandatory in EVA-3S and recommended in ICSS. Interestingly, there was a higher rate of stroke in the patients treated with a protection device than those treated without in SPACE (Jansen *et al.* 2009). ICSS also showed that protection devices had a higher complication rate than patients treated without protection device (Doig *et al.* 2010).

ICSS has confirmed suspicions raised by the Cochrane Review carried out in 2007 that surgery is superior to stenting in terms of short-term risk. Carotid endarterectomy should remain the treatment of choice of symptomatic carotid stenosis.

## 12 The Impact of Small Vessel Disease on The Outcome of Invasive Treatment of Carotid Artery Stenosis

### 12.1 Background

The large clinical trials of surgery have demonstrated that invasive treatment of symptomatic carotid stenosis prevents recurrent stroke (Barnett *et al.* 1998; Farrell *et al.* 1998; Rothwell *et al.* 2003). To a lesser extent trials of carotid endarterectomy in asymptomatic patients have also shown a benefit of surgery over medical treatment alone in preventing stroke (Toole *et al.* 1995; Halliday *et al.* 2004). However, while preventing stroke, surgery is itself a cause of stroke. In the 30 days following endarterectomy, 6.7% of patients recruited in NASCET and 7.0% of patients recruited in ECST had a stroke or died, while of the patients randomised to the control group, only 2.4% in NASCET and 0.2% in ECST had a stroke or died within 32 days after randomisation (Barnett *et al.* 1998; Farrell *et al.* 1998).

In the asymptomatic trials the rate of operative stroke or death was somewhat lower in both groups but nevertheless stroke occurred following surgery: 2.3% of patients randomised in ACAS and 2.8% of patients enrolled in ACST had a stroke or died in the 30-day period following carotid endarterectomy (Toole *et al.* 1995; Halliday *et al.* 2004). Only 0.4% of patients randomised to the control group in ACAS had a stroke or died in a similar time period following randomisation.

The large stenting trials confirmed the findings of the surgical trials and in addition showed that stenting carried a similar risk of post-procedural stroke, and depending on the trial even a significantly higher risk than surgery (Eckstein *et al.* 2008; Mas *et al.* 2008; Brott *et al.* 2010; Ederle *et al.* 2010).

It is not surprising that invasive treatment should carry a treatment-inherent risk. There is no reason why Paracelsius' axiom "*Dosis sola venenum facit*" (only the quantity makes



the poison) and the knowledge that there is no effect without side effect (“all things are poison and nothing is without poison”) should not apply to carotid endarterectomy or stenting. It is one of the aims of research and clinical practice to strive to improve the safety of any procedure. If factors contributing to the procedural risk could be identified and appropriate steps taken, safety may well be improved.

White matter changes are a common finding on computed tomography (CT) and magnetic resonance imaging (MRI) of the brain. They are prevalent in the elderly and seen particularly in patients with dementia and stroke (Pantoni *et al.* 1995; Streifler *et al.* 1995; Tarvonen-Schroder *et al.* 1996; Pantoni *et al.* 1997; Leys *et al.* 1999). The Framingham Heart Study has shown that severe cerebral white matter disease more than doubles the risk of future stroke (Debette *et al.* 2010). Vladimir Hachinski and his colleagues first proposed the term leukoaraiosis as a purely descriptive term for the presence of patchy diffuse low density changes in the cerebral white matter (Hachinski *et al.* 1987).

The pathophysiology of leukoaraiosis is complex and not entirely understood. Pathological studies have found enlarged perivascular spaces, gliosis, axonal loss, and myelin pallor in areas of leukoaraiosis (Caplan *et al.* 1978; Babikian *et al.* 1987). Recent studies have not shown any correlation of leukoaraiosis with myelin loss demonstrated with Luxol Fast Blue (LFB) or immunohistochemical staining and myelin loss may not be the direct pathologic correlate of leukoaraiosis (Young *et al.* 2008; Auriel *et al.* 2010).

Associated with areas of leukoaraiosis are changes in the structure of small perforating arteries and white matter changes can often be observed in patients with lacunar strokes (Wiszniewska *et al.* 2000). The finding of vessel wall-thickening associated with leukoaraiosis indicates that structural abnormalities of cerebral vessels are associated with the development of leukoaraiosis (Auriel *et al.* 2010). Increased vessel wall thickening and elevated immunoreactivity of hypoxia-inducible factors (HIF1 $\alpha$  and HIF2 $\alpha$ ) in deep sub cortical white matter lesions were demonstrated in an unselected cohort of the elderly providing evidence that hypoxia may contribute to the development

of leukoaraiosis (Fernando *et al.* 2006). This, together with a lack of association of leukoaraiosis with markers of systemic atherosclerosis, points towards longstanding haemodynamic hypoxia being the main cause for the development of leukoaraiosis (Auriel *et al.* 2010).

Cross-sectional imaging of brain is useful in evaluating the extent of white matter changes. A prevalence of leukoaraiosis between 4% and 44% using CT and up to 100% on MRI has been reported in stroke patients, the latter owing to its higher sensitivity and depending on patient selection (Streifler *et al.* 1995; Pantoni *et al.* 1997; Leys *et al.* 1999). The incidence of white matter changes increases with age and some changes are usual above the age of 40 years. Other risk factors for the development of white matter changes include hypertension and leukoaraiosis is associated with cognitive impairment and dementia (Jeerakathil *et al.* 2004; Verdelho *et al.* 2010).

Jonathan Streifler demonstrated that white matter changes were associated with a higher perioperative risk of stroke or death in patients assigned to carotid endarterectomy in NASCET (Streifler *et al.* 2002). Patients with widespread white matter changes allocated to the control group also had an increased risk of stroke or death. To date, the influence of white matter changes on the procedural risk of stroke and death in carotid stenting has not been investigated.

The study described in this chapter was therefore carried out to investigate the influence of leukoaraiosis on the risk of procedural complications in a large patient group with recently symptomatic carotid disease.

## 12.2 Methods

### 12.2.1 Patients and Centre Requirements

All patients included in this study were enrolled in the International Carotid Stenting Study (ICSS), which was described in detail in the previous chapter and the results of the main short-term analysis were published recently (Ederle *et al.* 2010). ICSS is an

international multi-centre randomised clinical trial comparing carotid stenting and endarterectomy in patients with symptomatic carotid atheromatous disease. All patients participating in ICSS provided written informed consent.

Patients were randomised at 50 centres in Europe, Canada, Australia and New Zealand with a team in place at each centre consisting of a neurologist or physician with a special interest in stroke medicine, a designated surgeon with experience in endarterectomy and an interventionist with expertise in carotid stenting. Centres with little experience in either endarterectomy or stenting were enrolled as supervised centres and proctored until the Steering Committee was satisfied that a sufficient level of experience was achieved to carry out the procedure safely.

Patients over the age of 40 years were eligible to be enrolled in ICSS if they had symptomatic atheromatous carotid artery disease greater than 50%, measured by NASCET criteria or a non-invasive equivalent imaging technique (Barnett *et al.* 1998). They had to be equally suitable for surgery and stenting and deemed in need of invasive treatment. Patients were randomised using a computerised service provided by the Oxford Clinical Trials Service Unit.

As part of the pre-treatment work up, brain imaging (CT or MRI) was carried out to exclude other pathology and serve as baseline for comparison with subsequent brain imaging.

Patients were followed up by an independent neurologist or physician with an interest in stroke medicine one month after treatment, six months and annually after randomisation. Long-term follow-up is ongoing.

All patients randomised in ICSS were eligible for the study of white matter changes. They were included in the analysis if baseline CT or MRI prior to study treatment was available at the Central Trial Office. Patients were excluded if no baseline brain imaging was available or if the quality was poor.

### 12.2.2 Definition of Outcome Events

Stroke was defined as an acute disturbance of focal neurological function with symptoms lasting more than 24 hours resulting from intracranial vascular disturbance. Visual loss resulting from embolic or haemodynamic retinal ischaemia lasting more than 24 hours was included in this category. Events leading to a modified Rankin score of 3 or greater for more than 30 days after onset were classified as disabling and the remaining events were classified as non-disabling. Events leading to death within 30 days after onset were classified as fatal.

Myocardial infarction was defined by the presence of a combination of two out of three of the following criteria:

- Specific cardiac enzymes more than twice the upper limit of normal
- A history of chest discomfort for at least half an hour
- The development of specific abnormalities on a standard 12-lead ECG (e.g. Q waves)

A procedural event was defined as an event occurring within 30 days of treatment.

### 12.2.3 Outcome Measures

For the purpose of this study the main outcome measure was defined as:

- Any stroke, death, or procedural MI

This was also the main outcome measure of the short-term analysis of ICSS described in the previous chapter (Ederle *et al.* 2010).

Additional outcome measures were defined prior to the analysis of data and excluded myocardial infarction:

- Any stroke or death
- Any stroke

- Disabling or fatal stroke

Events were measured at 120 days after randomisation and analysed by intention to treat.

#### 12.2.4 Rating of White Matter Changes

Anonymised diagnostic brain imaging prior to treatment were collected at the Central Trial Office. Two investigators trained in the analysis of white matter changes and blinded to treatment and clinical outcome rated all images by consensus using the age-related white matter changes (ARWMC) score first introduced and validated for the use in CT and MRI by Lars Wahlund and his colleagues (Wahlund *et al.* 2001).

The degree of white matter disease was rated on a 4-point scale in different brain regions on T2-weighted and FLAIR MRI images or on CT images. In patients in whom both imaging modalities had been carried out, MRI was chosen for rating white matter changes.

White matter changes in the cerebral hemispheres and the brainstem were defined as poorly defined hyperintensities  $\geq 5$  mm along the maximum diameter on T2-weighted or FLAIR MRI images and areas of poorly defined hypodensity of 5 mm or more on CT. Changes in the basal ganglia were rated in the same manner. The rating scale definitions are displayed in Table 12.1. Infarcts were excluded.

Five brain regions were scored in each patient separately in the left and right hemispheres:

- The **frontal area**: This was the frontal lobe anterior to the central sulcus
- The **parieto-occipital area** consisted of the parietal and occipital lobes in combination
- The **temporal area** was the temporal lobe, with a line from the posterior part of the Sylvian fissure to the trigones of the lateral ventricles separating this area from the parieto-occipital area

- The **infratentorial area** included the brain stem and cerebellum
- The **basal ganglia** included the striatum, globus pallidus, thalamus, external capsules and insula

The total age-related white matter changes score was then obtained by adding the scores for each brain region. Thus the total ARWMC score ranged from 0 to 30.

*Table 12.1 – ICSS-ARWMC: The Age-related white matter changes (ARWMC) rating scale for MRI and CT*

---

**White matter lesions**

|   |   |
|---|---|
| 0 | No lesions (including symmetrical, well-defined caps or bands)                    |
| 1 | Focal lesions   |
| 2 | Beginning confluence of lesions   |
| 3 | Diffuse involvement of the entire region, with or without involvement of U fibres |

**Basal ganglia lesions**

|   |                               |
|---|-------------------------------|
| 0 | No lesions                    |
| 1 | 1 focal lesion ( $\geq 5$ mm) |
| 2 | > 1 focal lesion              |
| 3 | Confluent lesions             |

---

In addition to the rating of white matter changes, the presence of established cerebral infarcts was noted.

Due to the nature of the trial as an international multicentre trial different scanners and scanning protocols were used. Studies available on film were rated using standardised diagnostic grade light boxes. Digital imaging was reviewed using an open-source DICOM viewer software (OsiriX version 3.x, OsiriX Foundation, [www.osirix-viewer.com](http://www.osirix-viewer.com)).

### 12.2.5 Hypothesis and Statistical Analysis

The hypothesis for this study was that white matter changes are associated with an increased risk of an unfavourable outcome after stenting and carotid endarterectomy. The analysis of white matter changes was not pre-specified in the study protocol and no separate power calculation had been carried out.

Because this was a subgroup analysis of a non-randomised comparison, baseline characteristics of patients allocated stenting and carotid endarterectomy were compared using the Mann-Whitney U-test for non-parametric variables and Chi-square tests for categorical variables. The age-related white matter score in both groups was compared using the independent samples t-test.

Some patients in ICSS did not receive their allocated treatment. All randomised patients included in this study were compared in an intention-to-treat analysis based on 120 days of follow-up regardless of whether they received the allocated treatment or not.

The overall 120-day risk of an outcome event was tested for the whole population (regardless of treatment allocation) using a Cox regression model with the age-related white matter score as continuous variable (i.e. intention to treat) to investigate the overall influence of white matter changes on the risk of procedural complications. Subsequently, the cumulative incidences of the different outcome measures were estimated using log-rank tests stratified by treatment using the age-related white matter score with cut-offs chosen at the 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> quartile and dichotomised at the median.

All analyses were adjusted for age to account for the fact that white matter changes are related to the age of the patient.

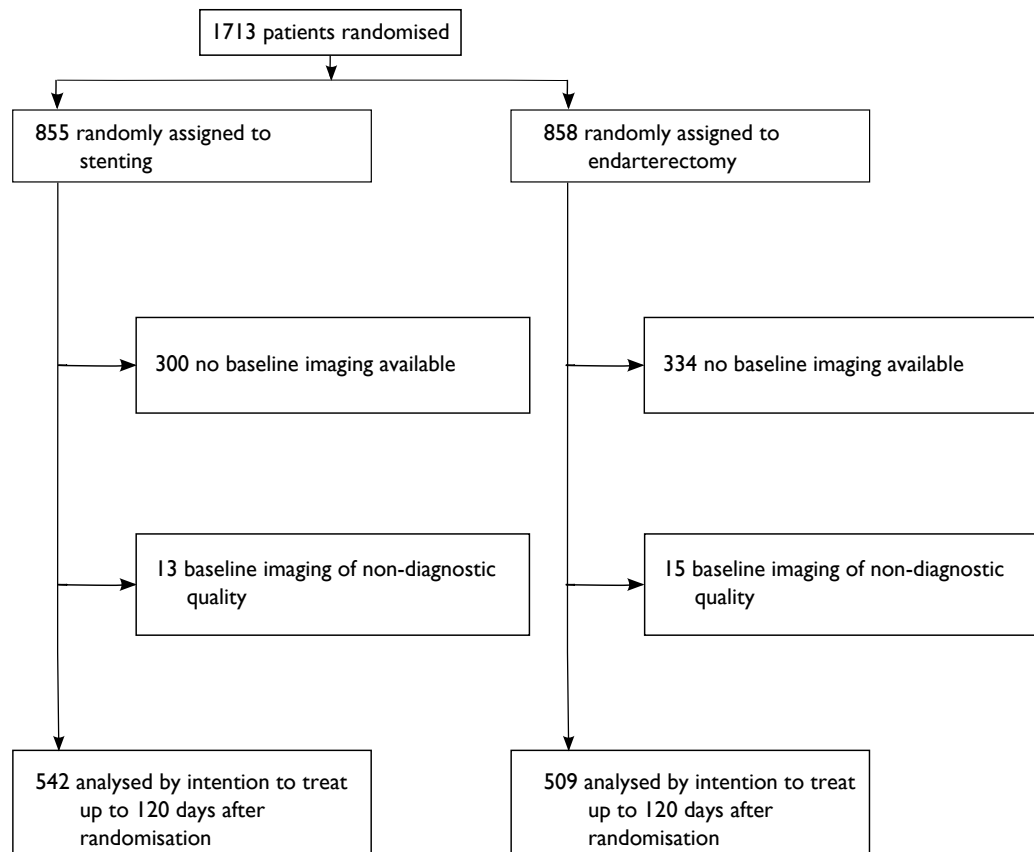
## 12.3 Results

### 12.3.1 Baseline Patient Data

Baseline brain imaging prior to treatment was available in 1,051 patients enrolled in ICSS and included in this study (Figure 12.1). Of the total number of patients enrolled in ICSS,

67% of the patients in the stenting group (n = 542) and 59% of the patients in the surgery group (n = 509) had suitable brain imaging. Just over half of the scans had been carried out using CT (53% in the stenting group and 56% in the surgery group,  $p = 0.45$ ).

Figure 12.1 – ICSS-ARWMC: Trial profile



The time between scan and treatment was significantly shorter in the stenting arm than in the surgery group (16 days versus 23 days, respectively,  $p < 0.0001$ ).

Baseline patient characteristics did not differ significantly between the two groups. The risk factors generally thought to influence small vessel disease in particular such as age, hypertension, and hypercholesterolaemia were distributed equally in both groups.



**Table 12.2 – ICSS-ARWMC: Patient characteristics at baseline per allocated treatment**

Data are number of patients (% of known data), unless otherwise indicated. CEA, carotid endarterectomy; BP, blood pressure; SD, standard deviation. \*Degree of stenosis measured by NASCET method at randomising centre. †If two events were reported on the same day, the more serious of the two was counted (stroke>retinal infarct>TIA>A fugax). ‡P values are calculated using Fisher's exact test or Pearson's Chi-square test for categorical variables and the Mann-Whitney U-test for non-categorical variables (table continued on next page).

|  | Stenting<br>(n = 542) | CEA<br>(n = 509) | P<br>Value‡ |
|--|-----------------------|------------------|-------------|
| <b>CT scan</b>                                 | 288 (53%)             | 285 (56%)        | 0.441       |
| <b>Age (mean [SD], years)</b>                  | 70 [9]                | 70 [9]           | 0.753       |
| <b>Sex</b>                                     |                       |                  |             |
| Women  | 252 (30%)             | 251 (29%)        | 0.684       |
| <b>Vascular risk factors</b>                   |                       |                  |             |
| Cerebral infarct on baseline scan              | 278 (51%)             | 252 (49%)        | 0.830       |
| Hypertension                                   | 384 (72%)             | 350 (69%)        | 0.340       |
| Systolic blood pressure (mean [SD], mmHg)      | 147.9 [25.2]          | 146.2 [23.4]     | 0.344       |
| Diastolic blood pressure (mean [SD], mmHg)     | 79.6 [12.4]           | 78.1 [12.5]      | 0.095       |
| Diabetes mellitus                              | 120 (23%)             | 105 (21%)        | 0.491       |
| Hyperlipidaemia                                | 338 (63%)             | 332 (66%)        | 0.476       |
| Cholesterol (mean [SD], mmol/L)                | 4.8 [1.2]             | 4.9 [1.3]        | 0.302       |
| Current smoker                                 | 120 (23%)             | 111 (22%)        | 0.881       |
| Past smoker                                    | 267 (50%)             | 262 (52%)        | 0.587       |
| Peripheral vascular disease                    | 91 (17%)              | 78 (8%)          | 0.501       |
| <b>Degree of symptomatic carotid stenosis*</b> |                       |                  | 0.252       |
| 50-69%   | 70 (13%)              | 54 (11%)         |             |
| 70-99%   | 472 (87%)             | 455 (89%)        |             |
| <b>Degree of contralateral stenosis*</b>       |                       |                  | 0.379       |
| <50%   | 365 (67%)             | 331 (65%)        |             |
| 50-69%   | 78 (14%)              | 81 (16%)         |             |

|  | Stenting<br>(n = 542) | CEA<br>(n = 509) | P<br>Value‡ |
|--|-----------------------|------------------|-------------|
| 70-99%   | 64 (12%)              | 74 (15%)         |             |
| Occluded   | 31 (6%)               | 21 (4%)          |             |
| Unknown  | 4 (1%)                | 2 (0.4%)         |             |
| <b>Most recent ipsilateral event†</b>                            |                       |                  | 0.845       |
| Amaurosis fugax  | 84 (16%)              | 79 (16%)         |             |
| Transient ischaemic attack                                       | 175 (32%)             | 175 (34%)        |             |
| Ischaemic hemispheric stroke                                     | 262 (48%)             | 241 (47%)        |             |
| Retinal infarct  | 13 (2%)               | 9 (2%)           |             |
| Unknown  | 8 (2%)                | 5 (1%)           |             |
| <b>Multiple ipsilateral symptoms prior to randomisation</b>      | 221 (41%)             | 194 (38%)        | 0.413       |
| <b>Ipsilateral stroke prior to most recent ipsilateral event</b> | 92 (17%)              | 68 (13%)         | 0.124       |

Table 12.2 continued

### 12.3.2 Age-related White Matter Changes Score

The mean total age-related white matter changes score was similar in both groups ( $7.11 \pm 4.43$  in the stenting group and  $7.03 \pm 4.62$  in the surgery group,  $p = 0.637$ ). The distribution of ARWMC score in the different brain regions did not differ between the two treatment groups, with the frontal brain region being the most common site of small vessel disease (Table 12.3).

Table 12.3 – ICSS-ARWMC: Rating scores (mean  $\pm$  SD) according to location and treatment

Data are mean  $\pm$  SD. CEA, carotid endarterectomy (table continued on next page).

|                | Stenting<br>(n = 542) | CEA<br>(n = 509) | P<br>Value* |
|----------------|-----------------------|------------------|-------------|
| <b>Frontal</b> |                       |                  |             |
| Ipsilateral    | $1.22 \pm 0.71$       | $1.19 \pm 0.69$  | 0.398       |
| Contralateral  | $1.15 \pm 0.71$       | $1.14 \pm 0.70$  | 0.569       |

|                          | Stenting<br>(n = 542) | CEA<br>(n = 509) | P<br>Value* |
|--------------------------|-----------------------|------------------|-------------|
| <b>Parieto-occipital</b> |                       |                  |             |
| Ipsilateral              | 1.04 ± 0.83           | 1.00 ± 0.80      | 0.356       |
| Contralateral            | 1.01 ± 0.83           | 0.94 ± 0.80      | 0.114       |
| <b>Temporal</b>          |                       |                  |             |
| Ipsilateral              | 0.23 ± 0.44           | 0.26 ± 0.45      | 0.340       |
| Contralateral            | 0.23 ± 0.43           | 0.25 ± 0.45      | 0.445       |
| <b>Infratentorial</b>    |                       |                  |             |
| Ipsilateral              | 0.20 ± 0.44           | 0.18 ± 0.43      | 0.497       |
| Contralateral            | 0.19 ± 0.44           | 0.19 ± 0.46      | 0.817       |
| <b>Basal Ganglia</b>     |                       |                  |             |
| Ipsilateral              | 0.94 ± 0.93           | 0.97 ± 0.91      | 0.996       |
| Contralateral            | 0.90 ± 0.89           | 0.92 ± 0.94      | 0.988       |
| <b>Total ARWMC score</b> | 7.11 ± 4.43           | 7.03 ± 4.62      | 0.637       |

*Table 12.3 continued*

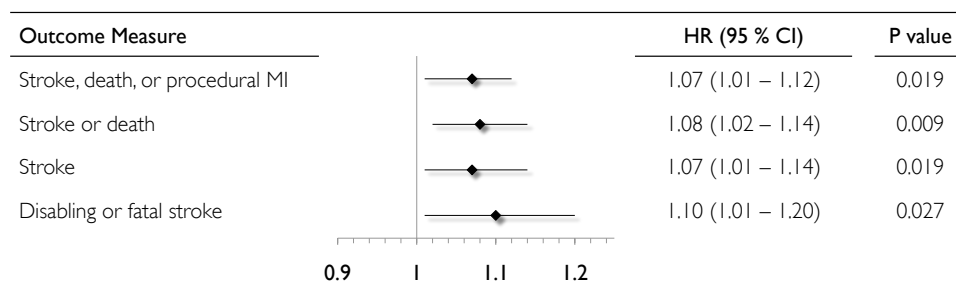
### 12.3.3 Analysis of ARWMC Score

#### The ARWMC Score in the Population as a Whole

Pooling both treatment groups together and adjusting for age, white matter disease as expressed by the total age-related white matter changes score was significantly associated with an increased the risk of stroke, death, or procedural MI at 120 days after randomisation. The hazard ratio associated with an increase in ARWMC score of one point was 1.07 (95% CI 1.01 to 1.12,  $p = 0.019$ , Figure 12.2). White matter disease was also significantly associated with an increased risk of stroke or death (HR 1.08, 95% CI 1.02 to 1.14,  $p = 0.009$ ), stroke (HR 1.07, 95% CI 1.01 to 1.14,  $p = 0.019$ ) and disabling or fatal stroke (HR 1.10, 95% CI 1.01 to 1.20,  $p = 0.027$ , Figure 12.2).

**Figure 12.2 – ICSS-ARWMC: Hazard ratios for total ARWMC score**

Shown are the hazard ratios for each outcome measure associated with a 1-point increase in ARWMC score. HR, hazard ratio; CI, confidence interval; MI, myocardial infarction.



### The ARWMC Score in Quartiles per Treatment Group

#### Stroke, Death, or Procedural Myocardial Infarction

The cumulative incidence of stroke, death, or procedural myocardial infarction at 120 days after randomisation increased with each quartile of total ARWMC score. In the stenting group, the estimated cumulative incidence of stroke, death or procedural MI was 5.4% (SE 2.1%) in patients in the 1<sup>st</sup> quartile, i.e. with an ARWMC score < 4 (6 events in 112 patients), 3.8% (SE 1.5%, 6 events in 158 patients) in patients in the 2<sup>nd</sup> quartile (ARWMC score ranging from 4 to 6), 11.1% (SE 3.0%, 12 events in 108 patients) in patients in the 3<sup>rd</sup> quartile (ARWMC score ranging from 7 to 9), and 13.5% (SE 2.7%, 22 events in 164 patients) in patients in the 4<sup>th</sup> quartile (ARWMC score ≥ 10). This increase was statistically significant (log-rank  $p = 0.008$ ). In the surgery group, the cumulative incidence of stroke, death or procedural myocardial infarction at 120 days after randomisation was more evenly distributed between the four groups of ARWMC score and was estimated at 3.4% (SE 1.7%, 4 events in 119 patients), 4.3% (SE 1.7%, 6 events in 141 patients), 4.8% (SE 2.1%, 5 events in 105 patients), and 6.3% (SE 2.0%, 9 events in 145 patients) in the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, and 4<sup>th</sup> quartile of total ARWMC score respectively. The increase in cumulative incidence in the surgery group was not statistically significant (log-rank  $p = 0.730$ , Figure 12.3).

### Stroke or Death

A similar result was obtained for the cumulative incidence of stroke or death 120 days after randomisation. There was an increase in cumulative incidence in the stenting group from 5.4% (SE 2.1%, 6 events) in the 1<sup>st</sup> quartile to 13.5% (SE 2.7%, 22 events) in the 4<sup>th</sup> quartile (log-rank  $p = 0.008$ ), while in the surgery group the cumulative incidence between quartiles of ARWMC score in the first quartile (2.5%, SE 1.4%, 3 events) and in the fourth quartile (5.6%, SE 1.9%, 8 events) was similar (log-rank  $p = 0.643$ , Figure 12.4).

### Stroke

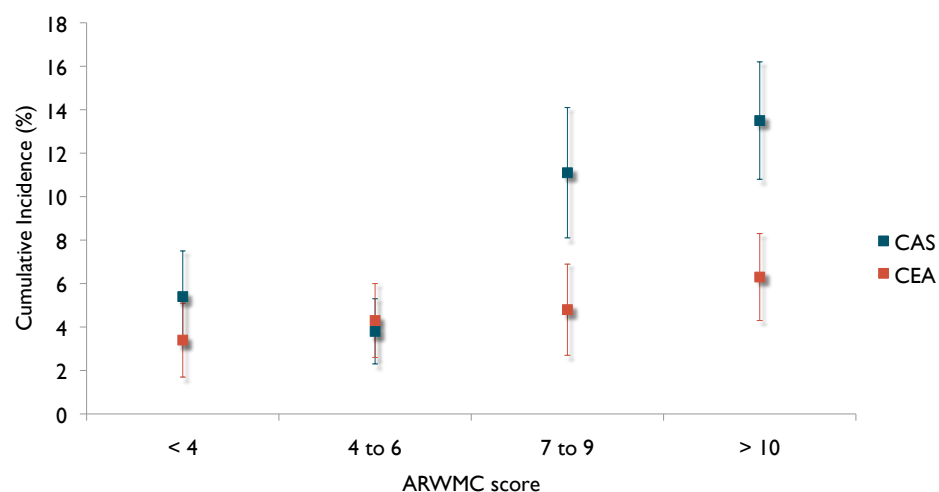
The pattern of a significant increase in cumulative incidence 120 days after randomisation with increasing quartile of total ARWMC score in the stenting group and more evenly balanced cumulative incidences in the quartiles of total ARWMC score in the surgery group was also observed for the separate analyses of stroke. In the stenting group the cumulative incidence in the 1<sup>st</sup> quartile was 4.5% (SE 2.0%) and increased to 12.3% (SE 2.6%) in the 4<sup>th</sup> quartile ( $p = 0.006$ ). In the surgery group there was a more modest and non-significant increase from 2.5% in the 1<sup>st</sup> quartile (SE 1.4%) to 4.9 (SE 1.8%) in the 4<sup>th</sup> quartile ( $p = 0.697$ , Figure 12.5).

### Disabling or Fatal Stroke

The cumulative incidence of disabling or fatal stroke increased from 0.9% (SE 0.9%, 1 event) in the 1<sup>st</sup> quartile to 6.1% (SE 1.9%, 10 events) in the stenting group ( $p = 0.018$ ). In the surgery group the cumulative incidence increased from 1.7% (SE 1.2%, 2 events) in the 1<sup>st</sup> quartile to 2.8% (SE 1.4%, 4 events) in the 4<sup>th</sup> quartile of ARWMC score (Figure 12.6).

**Figure 12.3 – ICSS-ARWMC: 120-day cumulative incidence of stroke, death or myocardial infarction per quartile of ARWMC score per treatment group**

Shown are Kaplan-Meier estimated cumulative incidences with their standard errors (vertical lines). CAS, carotid stenting; CEA, carotid endarterectomy, ARWMC, age-related white matter score; N, number of patients; n, number of events.

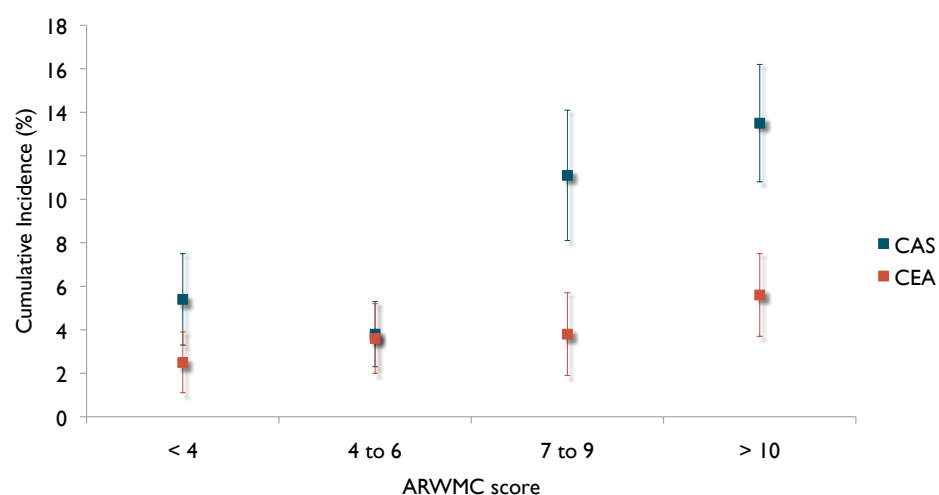


Patients and events:

|           |       |       |        |        |
|-----------|-------|-------|--------|--------|
| CAS (n/N) | 6/112 | 6/158 | 12/108 | 22/164 |
| CEA (n/N) | 4/119 | 6/141 | 5/104  | 9/145  |

**Figure 12.4 – ICSS-ARWMC: 120-day cumulative incidence of stroke or death per quartile of ARWMC score per treatment group**

Shown are Kaplan-Meier estimated cumulative incidences with their standard errors (vertical lines). CAS, carotid stenting; CEA, carotid endarterectomy, ARWMC, age-related white matter score; N, number of patients; n, number of events.

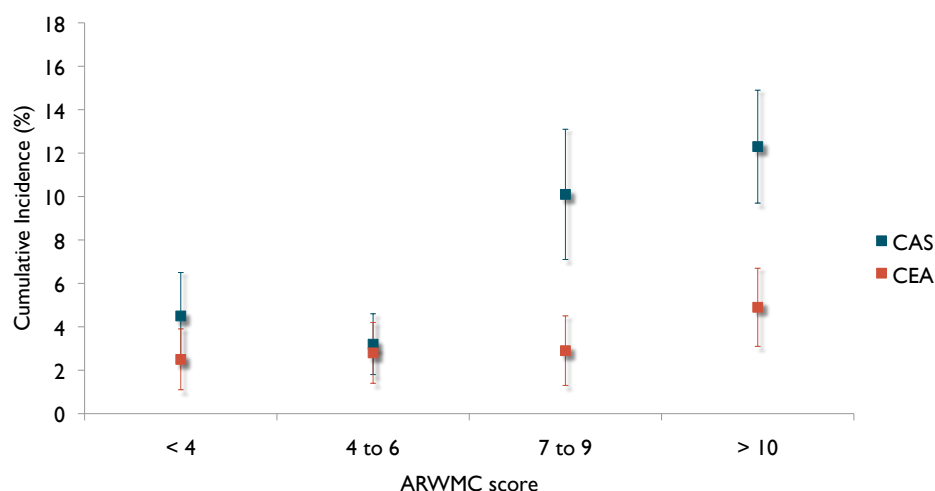


Patients at risk:

|           |       |       |        |        |
|-----------|-------|-------|--------|--------|
| CAS (n/N) | 6/112 | 6/158 | 12/108 | 22/164 |
| CEA (n/N) | 3/119 | 5/141 | 4/104  | 8/145  |

**Figure 12.5 – ICSS-ARWMC: 120-day cumulative incidence of stroke per quartile of ARWMC score per treatment group**

Shown are Kaplan-Meier estimated cumulative incidences with their standard errors (vertical lines). CAS, carotid stenting; CEA, carotid endarterectomy, ARWMC, age-related white matter score; N, number of patients; n, number of events.

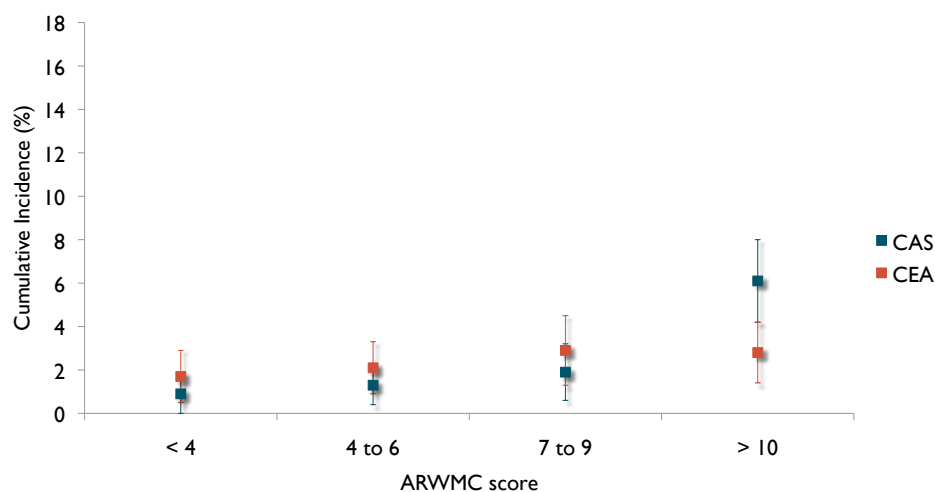


Patients at risk:

|           |       |       |        |        |
|-----------|-------|-------|--------|--------|
| CAS (n/N) | 5/112 | 5/158 | 12/108 | 20/164 |
| CEA (n/N) | 3/119 | 4/141 | 3/104  | 7/145  |

**Figure 12.6 – ICSS-ARWMC: 120-day cumulative incidence of disabling or fatal stroke per quartile of ARWMC score per treatment group**

Shown are Kaplan-Meier estimated cumulative incidences with their standard errors (vertical lines). CAS, carotid stenting; CEA, carotid endarterectomy, ARWMC, age-related white matter score; N, number of patients; n, number of events.



Patients at risk:

|           |       |       |       |        |
|-----------|-------|-------|-------|--------|
| CAS (n/N) | 1/112 | 1/158 | 2/108 | 10/164 |
| CEA (n/N) | 2/119 | 3/141 | 3/104 | 4/145  |

## Risk of Outcome by Treatment Group in the Upper and Lower 50<sup>th</sup> Percentile of ARWMC Score

### Stroke, Death, or Procedural Myocardial Infarction

Patients allocated to stenting and a total ARWMC score of  $\geq 7$  (median) had a significantly higher risk of stroke, death, or procedural MI than those patients with a total ARWMC score of less than 7. Stroke, death, or procedural MI occurred in 12 patients with an ARWMC score less than 7, and in 34 patients with an ARWMC score  $\geq 7$  in the stenting group. The cumulative incidence 120 days after randomisation was 4.5% (SE 1.3%) if the ARWMC score was less than 7 and 12.5% (SE 2.0%) with an ARWMC score  $\geq 7$  (HR 2.32, 95% CI 1.18 to 4.56,  $p = 0.014$ , Figure 12.7).

In the surgery group stroke, death, or procedural MI was recorded in 10 patients with an ARWMC score  $< 7$  and in 14 patients with an ARWMC score  $\geq 7$ . The risk of the same outcome associated with a total ARWMC score  $\geq 7$  (5.7%, SE 1.5%) in patients allocated surgery was not significantly higher than the risk associated with a low ARWMC score (3.9%, SE 1.2%). The hazard ratio was 1.48 (95% CI 0.62 to 3.56,  $p = 0.380$ ).

### Stroke or Death

The cumulative incidence of stroke or death was higher in patients allocated stenting with an ARWMC score in the upper 50 percentile, where it occurred in 34 patients (12.5%, SE 2.0%) than in patients with an ARWMC score in the lower 50 percentile, where stroke or death was recorded in 12 patients (4.5%, SE 1.3%, Figure 12.8). The hazard ratio was 2.32 (95% CI 1.18 to 4.55,  $p = 0.014$ ) and significantly favoured patients with a lower ARWMC score.

No significant difference between patients with an ARWMC score in the lower and upper 50 percentile was found for the risk of stroke or death in the surgery group (12 *versus* 8 events, respectively). The cumulative incidence was 3.1% (SE 1.1%) and 4.9% (SE 1.4 5), respectively (HR 1.84, 95% CI 0.70 to 4.84,  $p = 0.218$ ).



## Stroke

The same pattern was observed for stroke. In the stenting group there was a significant difference in cumulative incidence of stroke in patients with a ARWMC score less than 7 compared to patients with an ARWMC score  $\geq 7$ . In the former group, 10 patients suffered a stroke (3.7%, SE 1.2%) while the same outcome was recorded in 32 patients in the latter group (11.8%, SE 2.0%, Figure 12.9). The hazard ratio favoured the group of patients with a lower ARWMC score (HR 2.66, 95% CI 1.29 to 5.50,  $p = 0.008$ ).

In the surgery group no significant difference between patients with a low versus high ARWMC score was observed (ARWMC < 7: cumulative incidence 2.7%, SE 1.0%; ARWMC score  $\geq 7$ : cumulative incidence 4.0%, SE 1.3%, hazard ratio 1.79, 95% CI 0.63 to 5.11,  $p = 0.274$ ).

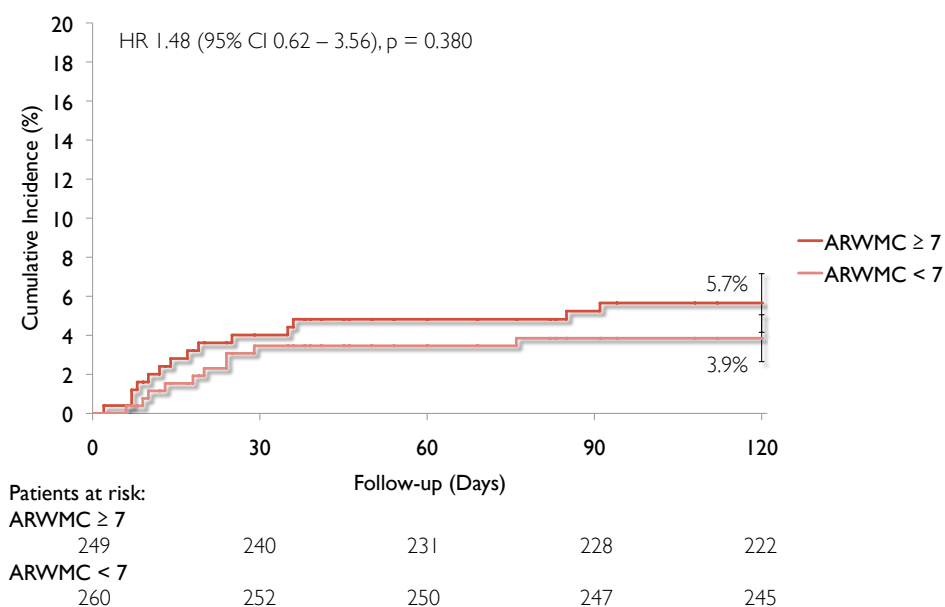
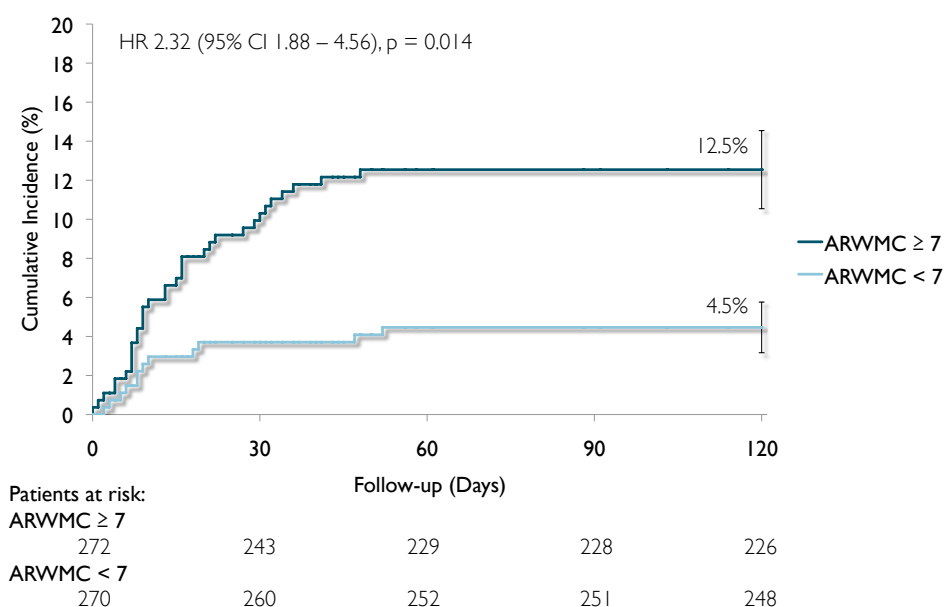
## Disabling or Fatal Stroke

Three patients who suffered a disabling or fatal stroke in the stenting group had an ARWMC score less than 7 compared to 12 patients with an ARWMC score  $\geq 7$  in the same treatment group suffering a disabling or fatal stroke (cumulative incidence 1.1%, SE 0.6% versus 4.4%, SE 1.2%, Figure 12.10). However, the hazard ratio showed no significant difference in the risk of disabling or fatal stroke in patients with a high or low ARWMC score (HR 2.72, 95% CI 0.76 to 9.94,  $p = 0.123$ ).

Similarly, in the surgery group the lower estimated cumulative incidence of disabling or fatal stroke in patients with an ARWMC score in the lower 50<sup>th</sup> percentile (1.9%, SE 0.9%) compared to patients with the ARWMC score in the upper 50<sup>th</sup> percentile (2.8%, SE 1.0%) was not associated with a significant difference in risk (HR 1.68, 95% CI 0.49 to 5.78,  $p = 0.415$ ).

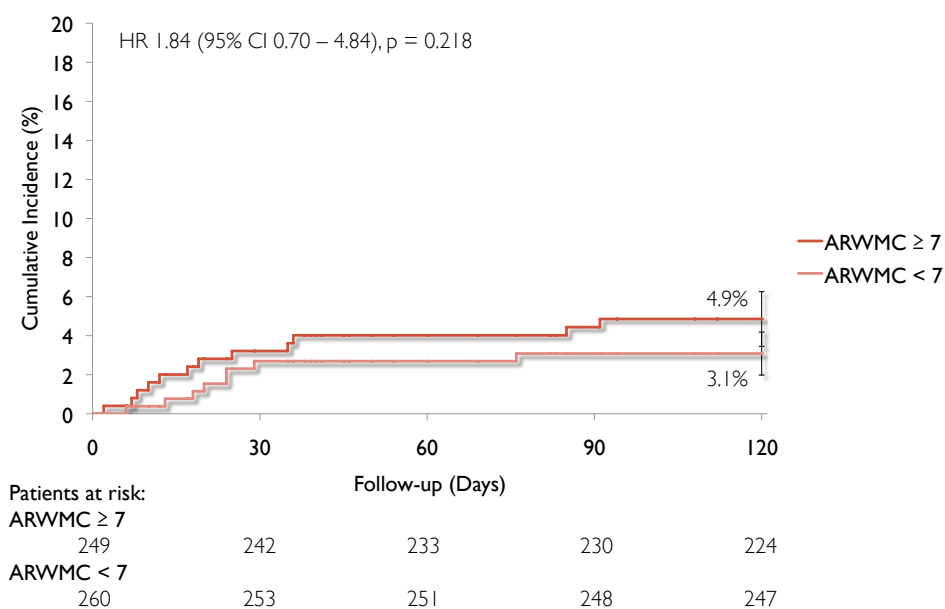
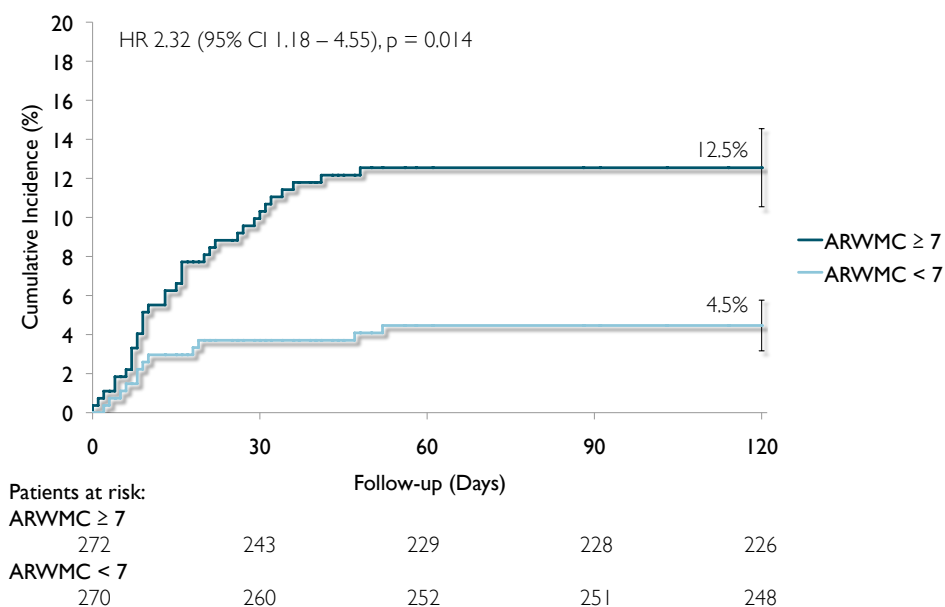
**Figure 12.7 – ICSS-ARWMC: Cumulative incidence of stroke, death or procedural MI according to extent of white matter changes**

Shown is the estimated 120-day Kaplan-Meier cumulative incidence in the stenting (top) and carotid endarterectomy group (bottom) with an age-related white matter changes (ARWMC) score < 7 and ≥ 7.



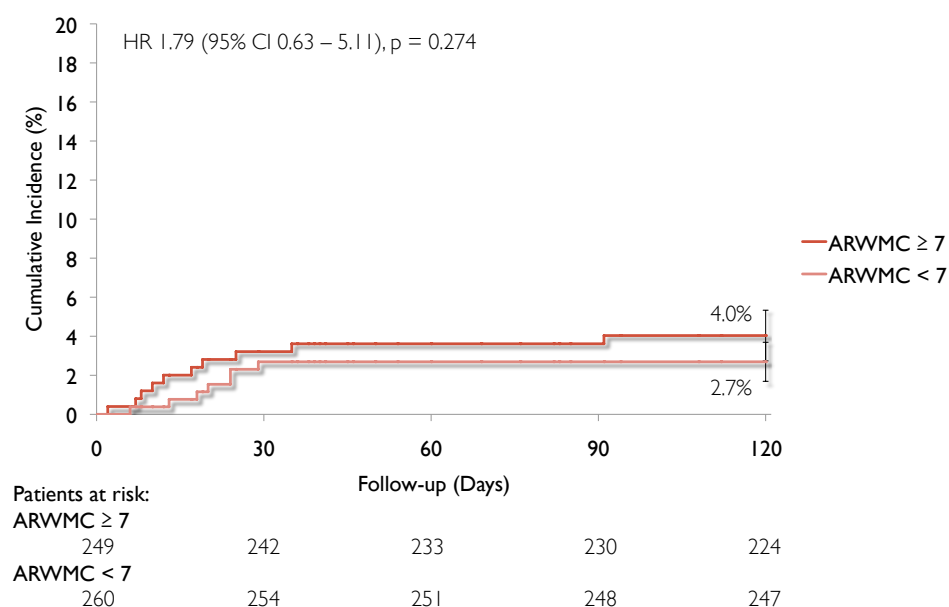
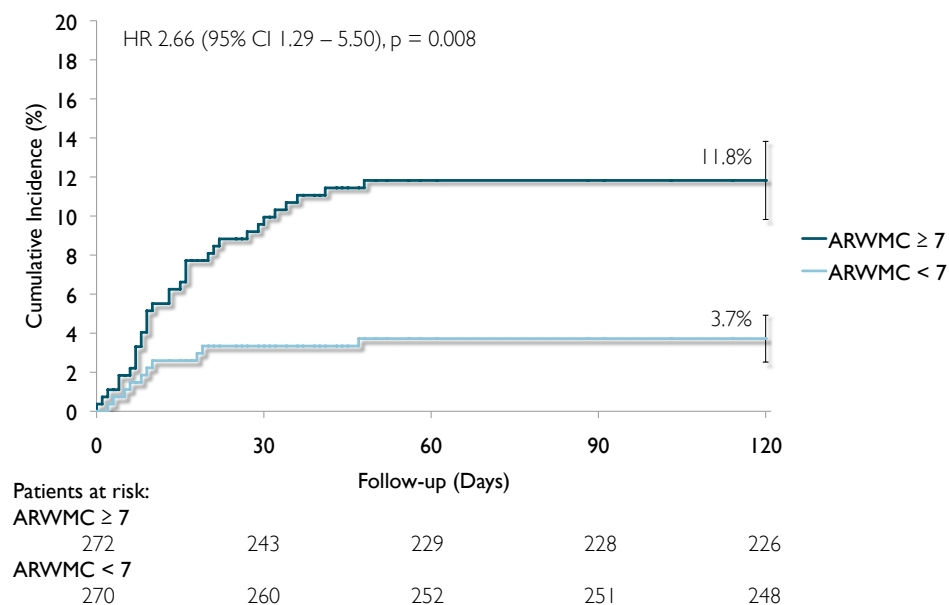
**Figure 12.8 – ICSS-ARWMC: Cumulative incidence of stroke or death according to extent of white matter changes**

Shown is the estimated 120-day Kaplan-Meier cumulative incidence in the stenting (top) and carotid endarterectomy group (bottom) with an age-related white matter changes (ARWMC) score < 7 and ≥ 7.



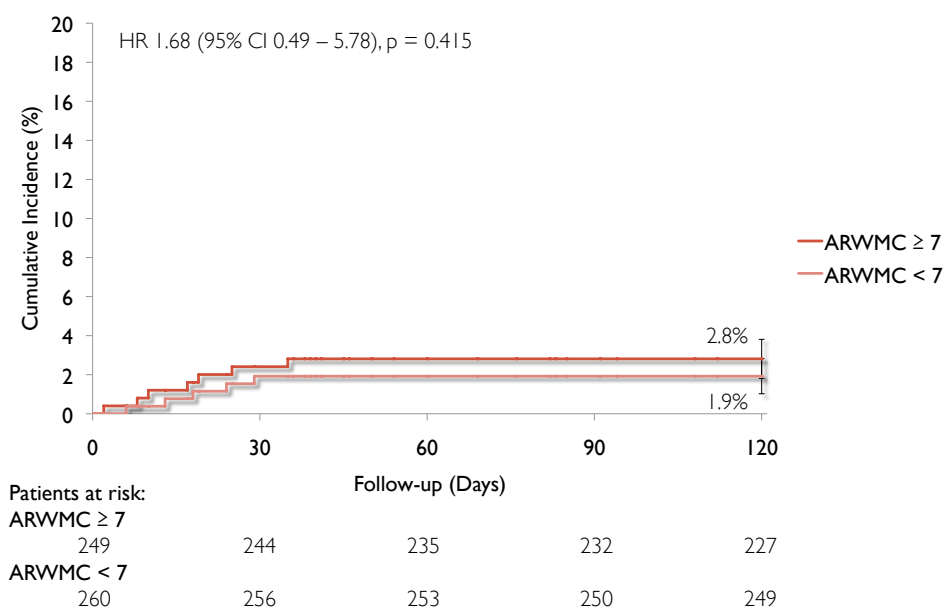
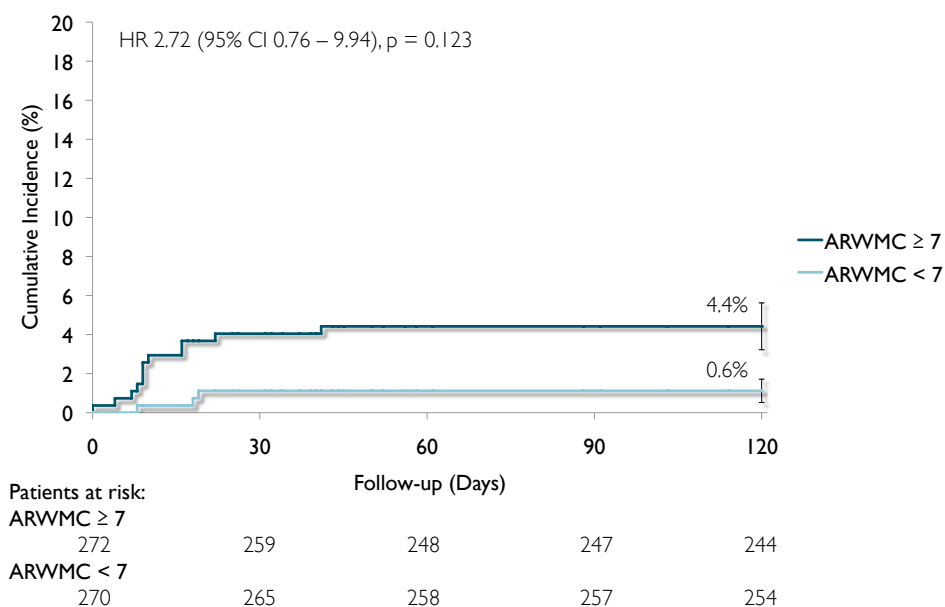
**Figure 12.9 – ICSS-ARWMC: Cumulative incidence of stroke according to extent of white matter changes**

Shown is the estimated 120-day Kaplan-Meier cumulative incidence in the stenting (top) and carotid endarterectomy group (bottom) with an age-related white matter changes (ARWMC) score < 7 and ≥ 7.



**Figure 12.10 – ICSS-ARWMC: Cumulative incidence of disabling or fatal stroke according to extent of white matter changes**

Shown is the estimated 120-day Kaplan-Meier cumulative incidence in the stenting (top) and carotid endarterectomy group (bottom) with an age-related white matter changes (ARWMC) score < 7 and ≥ 7.

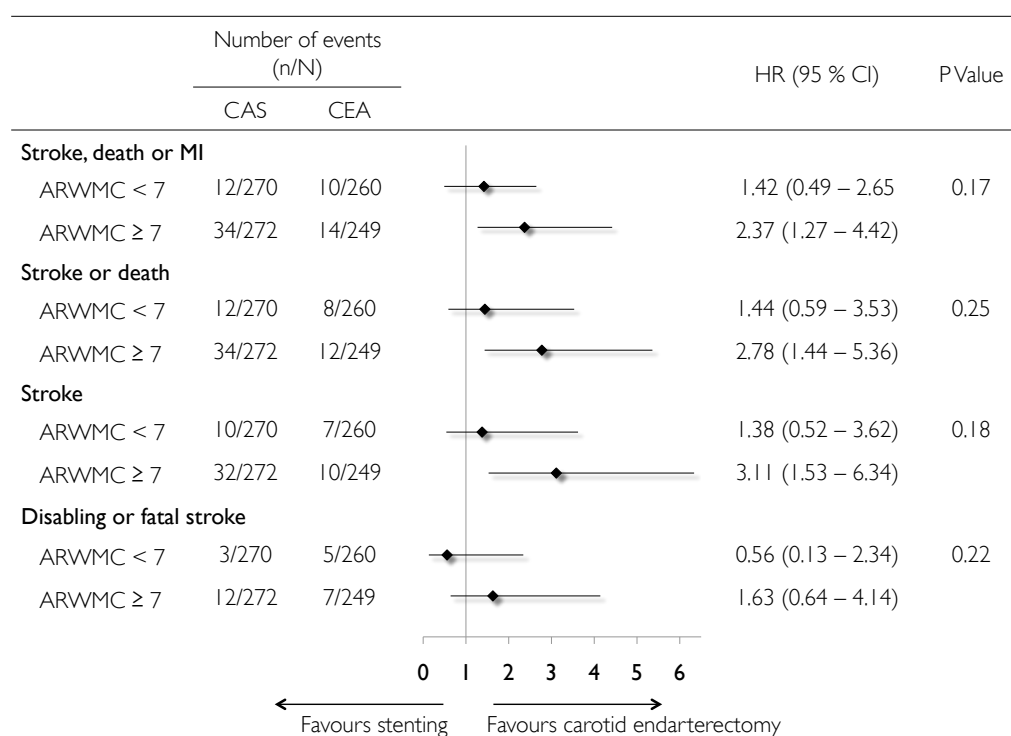


## Test for Treatment Interaction with ARWMC Score

The test for interaction between total ARWMC score and treatment showed that the increase in risk in patients with an ARWMC  $\geq$  7 in patients allocated to stenting compared to patients allocated to surgery that was observed in all outcome measures as described above was not statistically significant different (Figure 12.11).

**Figure 12.11 – ICSS-ARWMC: Hazard ratios (stenting versus endarterectomy) and 95% confidence intervals for various outcome measures in patients with age-related white matter changes scores below and above (and including) the median**

*P* values are associated with treatment-covariate interaction tests. ARWMC, age-related white matter changes; CAS, carotid stenting; CEA, carotid endarterectomy; MI, myocardial infarction; n, number of events; N, number of patients; HR, hazard ratio; CI, confidence interval.



## 12.4 Discussion

This is the first time the influence of age-related white matter changes on the procedural risk of stenting compared to surgery has been investigated in a large group of patients randomised in a clinical trial. The study showed that an increase in ARWMC score was associated with an increase in the risk of experiencing a procedural stroke, MI, or death.

In particular, patients with an ARWMC score in the upper 50<sup>th</sup> percentile the risk of experiencing an outcome event was higher than in those patients with an ARWMC score in the lower 50<sup>th</sup> percentile. This was more pronounced in patients who were randomised to stenting. However, the test for interaction between treatment and ARWMC score showed that the increase in risk comparing carotid artery stenting and endarterectomy in patients in the lower 50<sup>th</sup> percentile was not significantly different than the risk comparing stenting and endarterectomy in patients in the upper 50<sup>th</sup> percentile.

This study confirms findings by Jonathan Streifler and his colleagues in patients randomised in NASCET using a different rating method for white matter changes and who showed that the risk of perioperative stroke or death was associated with white matter changes (Streifler *et al.* 2002). However, the big increase in risk in patients with an ARWMC score in the upper 50<sup>th</sup> percentile assigned to stenting is striking.

The International Carotid Stenting Study found stenting to be associated with a higher risk of stroke, death, or procedural MI than surgery overall. The increase in risk associated with white matter changes may have contributed to the overall findings of ICSS.

Carotid Stenting is often carried out using cerebral filter devices that are designed to reduce the risk of embolisation to the brain. The ICSS MRI sub-study has shown that the risk of small emboli detected as changes on DWI MRI but not resulting in clinical deficits was higher in the stenting group compared to the surgery group (Bonati *et al.* 2010b). Together with the findings of this white matter study it seems to suggest that although

these micro-emboli may be asymptomatic at the time they occur, they pave the way for delayed cerebrovascular symptoms. This may be because of direct damage to blood vessels that directly lead to delayed symptoms. It is also feasible that any damage caused by micro-emboli and detected only on DWI leaves the vasculature and brain vulnerable to any ischaemia in the future because it reduces the brain and vasculature's ability to compensate for small brain ischaemia.

Although the study was a randomised comparison, the patients included in the white matter study were a selected sub-group of patients who had prior imaging. It is unlikely that this selection led to any bias, since the baseline characteristics were well matched between the two randomised groups in the white matter study and the white matter scores were also well balanced. However, the fact that it was a selected group of patients means that the sample size was smaller, thus limiting the power of the comparison. The number of outcome events in each group was small and the study was not designed to show small differences in risk associated with white matter changes.

The cerebrovascular risk factor profiles in both treatment groups were similar, particularly age, the presence of hypertension and hypercholesterolaemia, which are all thought to play a role in the development of white matter changes. This makes it less likely that the results can be attributed to differences in underlying risk factor profiles.

The rating score used in this analysis was first proposed and validated for use in MRI and CT by Lars Wahlund and his colleagues (Wahlund *et al.* 2001). The majority of brain imaging studies available in this comparison were acquired using CT and the extent of small vessel disease may be underestimated since the sensitivity of CT in detection white matter changes is lower than that of MR (Streifler *et al.* 1995; Pantoni *et al.* 1997; Leys *et al.* 1999). However, the proportion of CT studies in both treatment groups was similar and it is therefore unlikely to have introduced a significant bias in favour of one treatment.

As pointed out above, not all patients enrolled into ICSS had baseline brain imaging prior to treatment available for analysis. In many cases patients were referred for treatment



with the diagnosis of symptomatic carotid stenosis having been established elsewhere. It was felt unethical to repeat the brain imaging in these cases and although efforts were made to obtain copies of the brain imaging carried out prior to randomisation this was not successful in all cases. The study population available for the white matter changes study accounted for 60% of stroke, death, or procedural MI recorded in the entire ICSS population. This shortcoming may have limited the applicability of the results. While the estimated risk of stroke, death, or procedural MI in the entire ICSS population was exactly reproduced in the stenting group (8.5%), the estimated risk in the surgery group was slightly lower in this study population (4.7% compared to 5.2% in the entire ICSS population).

Despite these shortcomings, the white matter changes study carried out as part of the International Carotid Stenting Study (ICSS) provides valuable insight in the risk associated with age-related white matter changes. The study has confirmed earlier findings carried out in NASCET that white matter disease is associated with an increase in the procedural risk associated with carotid revascularisation of stroke or death or myocardial infarction, as well as stroke or death, stroke alone, and disabling or fatal stroke. The risk of an outcome event appears to be particularly high in the upper 50<sup>th</sup> percentile of total ARWMC score ( $\geq 7$ ) and while the increase in risk was bigger in patients assigned to stenting, the test for treatment interaction suggested that the increase in risk associated with stenting compared to endarterectomy was not significantly different between the group of patients with low ARWMC score of than and the group with scores greater than seven. Nevertheless, the increase in risk of stroke or death comparing stenting and endarterectomy was small in patients with an ARWMC score of less than seven (4.5% vs. 3.1%) which may justify considering stenting as an alternative to carotid endarterectomy in certain patients.

The pooled analysis of EVA-3S, SPACE, and ICSS has shown that age is an important predictor of risk of stenting (Bonati *et al.* 2010a). CREST also found that the age of the patients affected treatment efficacy, in that older patients undergoing carotid artery

stenting had a greater risk of suffering an adverse event (Brott *et al.* 2010). It is well documented that white matter disease becomes more prevalent with age (Breteler *et al.* 1994). The mean age of the patients was similar in both arms of the present study ( $70 \pm 9$  years,  $p = 0.753$ ), and the results therefore cannot be explained by differences in age in both treatment groups. In a sub study of ICSS, the number of patients with new ischaemic lesions on DWI-MRI post treatment was three times higher in the stenting arm than in the carotid endarterectomy arm, with the majority of lesions not resulting in a corresponding neurological deficit (Bonati *et al.* 2010b).

The pathophysiology of white matter changes is multi-factorial. They are often associated with demyelination and axon loss (Grinberg *et al.* 2010). Perivascular white matter lesions are frequently associated with both small and large vessel atherosclerotic disease (van Swieten *et al.* 1991; Chutinet *et al.* 2012). It has been suggested that white matter lesions are a result of chronic white matter hypoperfusion and changes in the blood-brain barrier that together lead to white matter rarefaction (Pantoni *et al.* 1997; O'Sullivan *et al.* 2002; Black *et al.* 2009; Topakian *et al.* 2010). White matter lesions are thought to be a risk factor for first ever and recurrent stroke (Fu *et al.* 2005; Enzinger *et al.* 2007; Simoni *et al.* 2010). This association can be explained in part by shared risk factors such as hypertension and chronically ischaemic brain may be more likely to develop infarction when exposed to further ischaemia (Grueter *et al.* 2012).

It was demonstrated using arterial spin-labeling MR perfusion that the extent of white matter lesions correlated with a reduction in cerebral blood flow (Bastos-Leite *et al.* 2008). Subjects with diffuse confluent white matter hyperintensities were found to have approximately 20% lower mean global cerebral blood flow than subjects with punctiform or beginning confluent white matter hyperintensities.

But rather than being a risk factor in its own right, white matter disease identified on brain imaging is likely to be a marker of cerebrovascular disease reflecting the overall effects of individual cardiovascular risk factors (Jeerakathil *et al.* 2004). A brain showing

signs of white matter disease and thereby demonstrating evidence of existing cerebrovascular disease may have less cerebrovascular reserve and be less able to cope with thrombotic material dislodged during carotid artery stenting, thus leading to stroke. This may explain the increased risk of procedural stroke, MI or death seen with increasing white matter changes overall, and in the stenting group in particular.

## 13 Discussion, Recent Developments, and Outlook

This thesis has described two major randomised clinical trials comparing endovascular treatment and endarterectomy in patients with symptomatic carotid artery stenosis, the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS) and the International Carotid Stenting Study (ICSS) and has put the results of these two trials into context of other large randomised trials identified through a comprehensive Cochrane Review. The research presented within the covers of this work spans almost 20 years of work by many collaborators in the field of carotid disease. The main findings of the thesis will now be summarised with the main research questions in mind. This will be followed by an outlook into the future of stroke research.

### 13.1 Summary of Main Results

CAVATAS was the first large trial that raised the possibility that endovascular treatment could be carried out with a similar short-term risk as carotid endarterectomy (Brown *et al.* 2001). This observation prompted other clinical trials that produced mixed results and failed to conclusively show endovascular treatment to be equivalent to surgery in terms of short-term risk (Naylor *et al.* 1998; Alberts 2001; Brooks *et al.* 2001; Yadav *et al.* 2004; Hoffmann *et al.* 2006; Mas *et al.* 2006; Ringleb *et al.* 2006). Remarkable is the fact that none of these trials favoured endovascular treatment.

The Cochrane Review carried out by this thesis' author highlighted the uncertainty surrounding endovascular treatment compared to surgery for symptomatic carotid artery disease (Ederle *et al.* 2007a). But it also highlighted how little consensus exists in the scientific community regarding terminology, choice of outcome events, length of follow up and presentation of data. It is accepted that the length of follow up primarily depends on the availability of funding. But why studies do not take into account other already published studies when writing up their own results, begs the question. Providing data for the same time points as previously published studies alongside their own chosen time points and outcome measures would be easy and help to compare studies. It is also very

unfortunate that some investigators included symptomatic and asymptomatic patients in the same trial without giving separate results for each group. The North American Carotid Revascularisation Endarterectomy *vs.* Stenting Trial (CREST) in particular suffered from the problem of combining both symptomatic and asymptomatic patients within a single study. Given that all evidence points towards these groups responding to treatment quite differently, this can only be explained by the need to increase patient recruitment in order to meet the targets identified in the design stage of the trial. This tends to unnecessarily muddy the waters and adds to the confusion and uncertainty surrounding best management of carotid artery disease.

Research into the field culminated in the publication of the International Stenting Study (Ederle *et al.* 2010). The authors demonstrated that up to 120 days after randomisation the policy of carotid endarterectomy was associated with a significantly lower risk of stroke, death or procedural MI (5.1% *vs.* 8.5%), any stroke (4.0% *vs.* 7.7%) and any stroke or death (4.6% *vs.* 8.5%) compared to carotid stenting. The absolute risk difference was small (3.4%), but the hazard ratio was significantly in favour of carotid endarterectomy (HR 1.73, 95% CI 1.18 to 2.52,  $p = 0.004$ ). In patients who received the allocated treatment the findings from the analysis including post-procedural events up to 30 days after treatment were very similar, suggesting that ICSS produced reliable and robust data. ICSS vindicated the results of the much-criticised EVA-3S study and together with SPACE accounts for almost 75% of patients contributing to the body of available evidence. Little doubt should be remaining that carotid endarterectomy is superior to carotid stenting in the short-term. What this result means for clinical practice, however, is less clear and will be explored further below.

CAVATAS is the only trial with truly long-term follow up data. It did not show a significant difference in the long term risk of disabling stroke or death, which was defined as the primary outcome measure (HR 1.02, 95% CI 0.79 to 1.32). Reviewers of the long term CAVATAS paper made much of the primary outcome definition and argued that mortality unrelated to the procedure should not have been included in the analysis

(unpublished personal communication). The reasons why this outcome has been chosen as the primary outcome measure have been set out in the relevant chapter and will not be repeated here. Excluding non-procedural mortality made little difference to the overall result, it still did not tip the balance in favour of either treatment. That none of the analyses favoured endovascular treatment is probably the more important message. Moreover, an extensive subgroup analysis comparing the risk of restenosis after either treatment points toward endovascular treatment as carrying a higher risk of restenosis greater than 70% and a higher rate of stroke associated with a high degree of restenosis. This makes it rather unlikely that, over the long term, stenting will be able to make up the ground it has lost in the initial 30 days after the procedure. Particularly since the often-cited improvements in stenting technology in terms of stent and guide wire design, which have become easier to use and deploy have thus far failed to translate into improvements in outcome.

Endovascular treatment and medical care were compared in patients who were not suitable for surgery (Ederle *et al.* 2009b). Unfortunately the trial only recruited a very small number of patients. Nevertheless, it is the largest randomised dataset available to date. Results of the trial were all associated with very large confidence intervals and one should refrain from forming firm conclusions from them.

The reasons for being not suitable for surgery are very limited, particularly since carotid endarterectomy can be safely carried out under local anaesthesia, as shown by the General Anaesthesia versus Local Anaesthesia for carotid surgery trial (GALA) (Lewis *et al.* 2008). Most patients today are likely to fulfil the inclusion criteria of the large trials (SPACE, EVA-3S, ICSS), a view shared and expressed by Peter Rothwell in a recent editorial in *The Lancet Neurology* (Rothwell 2009).

A study was carried out as part of ICSS that investigated the influence of small vessel disease on the risk of various procedural outcome measures. It showed that the risk of stroke, death, or procedural myocardial infarction up to 120 days after randomisation

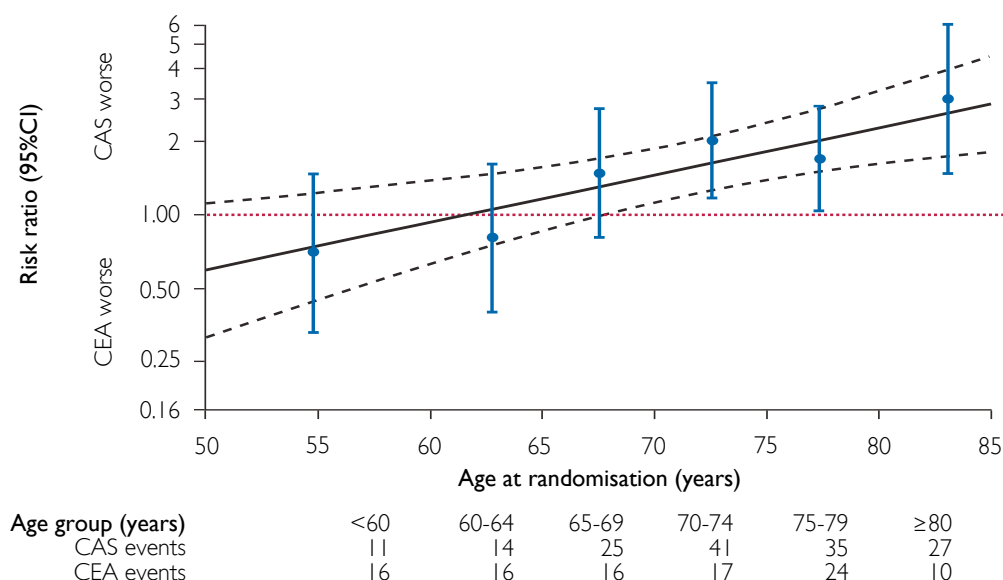
was associated with small vessel disease in both the stenting and carotid endarterectomy group. The risk was particularly high in patients with an age-related white matter changes score  $\geq 7$ , which was the median score in this study. The increase in risk associated with small vessel disease was greater in patients allocated stenting but the test for interaction between allocated treatment and ARWMC score showed that the increase in risk comparing carotid artery stenting and endarterectomy in patients in the lower 50<sup>th</sup> percentile was not significantly different than the risk comparing stenting and endarterectomy in the patients in the upper 50<sup>th</sup> percentile. Still, this study adds to the misery for stenting and helps to explain why this treatment is not as good as surgery in preventing stroke.

### 13.2 Recent Developments

Since the publication of ICSS more relevant data has become available. The Carotid Stenting Trialists' Collaboration (CSTC) was set up to perform a prospective meta-analysis of SPACE, EVA-2S, and ICSS and published their results in 2010 (Bonati *et al.* 2010a). It confirmed that stenting carried a significantly greater short-term risk of stroke or death than carotid endarterectomy. The absolute risk difference was 3% after 120 days and the analysis showed a relative risk increase of 50%. The results of ICSS (4% absolute risk increase for the same outcome) are broadly in line with the pooled meta-analysis. The risk associated with stenting was strongly dependent on age and doubled in patients older than 70 years while remaining similar in those patients younger than 70 years (Figure 13.1). The risk of stroke or death associated with carotid endarterectomy was similar in both age groups (Bonati *et al.* 2010a).

**Figure 13.1 – CSTC: Treatment risk ratios of any stroke or death within 120 days of randomisation by age (both continuous and by age groups)**

Analysis was by intention to treat. Blue dots and vertical bars represent treatment risk ratios and 95% confidence intervals, respectively, adjusted for source trial for each age group, with endarterectomy (CEA) as the reference group, plotted on a log scale at the mean age in each group. The continuous risk ratios by age (line) and 95% confidence intervals (dashed lines) were calculated by use of a binominal regression model containing treatment, continuous age, and their interaction, adjusted for source trial. CAS, carotid stenting. Reprinted from (Bonati et al. 2010a) with permission from Elsevier.



#### The North American Carotid Revascularisation Endarterectomy vs. Stenting Trial

(CREST) published its results in 2010. The trial included both symptomatic and asymptomatic patients. Overall, the reported risk of the composite primary endpoint of peri-procedural stroke, myocardial infarction, or death and post-procedural ipsilateral stroke after a median 2.5 years was similar in the stenting and endarterectomy groups (Brott *et al.* 2010). The CREST investigators concluded that stenting and endarterectomy were equivalent. It must be emphasised that this conclusion depends on the fact that, unlike in the European trials, patients were systematically screened for myocardial infarction. The reported myocardial infarction rates following carotid endarterectomy were much higher than reported in other trials, which did not screen for MI. On the other hand, MRI was not used to screen patients for cerebral infarction. ICSS showed that about three times more patients receiving carotid stenting than those undergoing carotid endarterectomy had new ischaemic lesions on DWI on post treatment MR scans

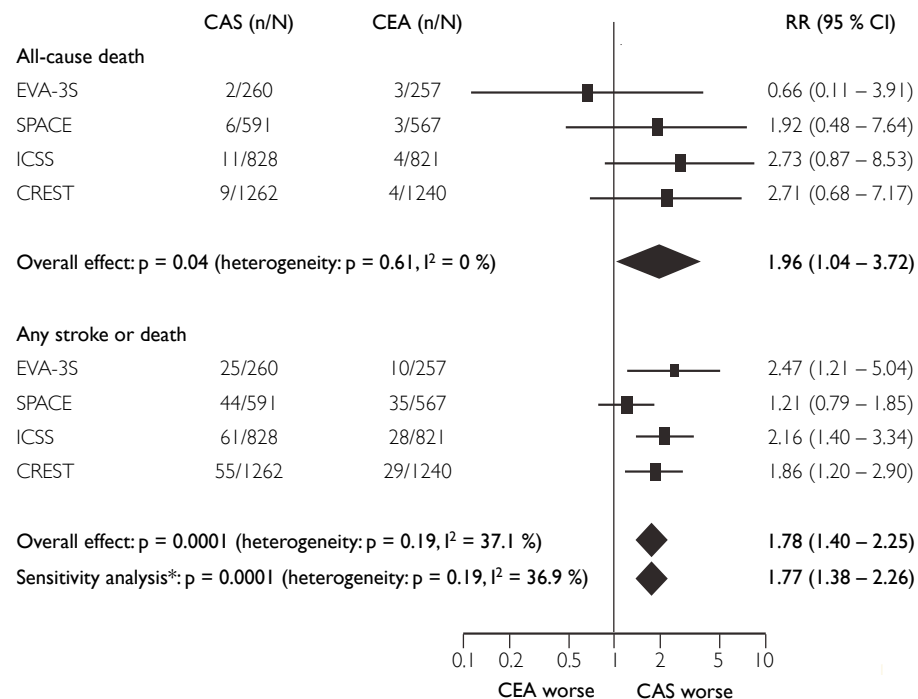


(Bonati *et al.* 2010b). The investigators have thus used double standards, on the one hand screening for (clinically silent) MI but not screening for (clinically silent) strokes. This in addition to the fact, that symptomatic patients were included alongside asymptomatic patients leaves CREST open to criticism.

Nevertheless, the risk of any peri-procedural stroke or death or post-procedural ipsilateral stroke was significantly higher in the stenting group compared to surgery (6% *vs.* 3.2%, hazard ratio 1.89, 95% CI 1.11 – 3.21,  $p = 0.02$ ) in CREST, thus confirming the results of ICSS and, as shown in Figure 13.2, broadly in line with the European trials (Amarenco *et al.* 2010).

**Figure 13.2 – CREST, EVA-3S, ICSS, and SPACE: Individual and pooled relative risks of death and of combined stroke and death within 30 days of randomisation**

Pooled relative risks (RR) were calculated with fixed-effects model. Data for EVA-3S, SPACE, and ICSS were extracted from per-protocol analysis of Carotid Stenting Trialists' Collaboration meta-analysis (Bonati *et al.* 2010a). CEA, carotid endarterectomy; CAS, carotid stenting. \*Sensitivity analysis excluding subgroup of asymptomatic patients enrolled in CREST. Reprinted from (Amarenco *et al.* 2010) with permission from Elsevier.



### 13.3 Translating Trial Results Into Clinical Practice

The findings of this thesis raise the question what this means for clinical practice. The results of ICSS are applicable to the current practice of carotid stenting at most vascular centres. The participating centres were representative of academic centres with substantial experience of treating carotid stenosis and had to show a high standard of practice before they could join the trial. The main lesson to be drawn for day-to-day clinical care of patients with symptomatic patients is that carotid endarterectomy is and should remain the treatment of choice in patients with symptomatic carotid stenosis. However, several points need be borne in mind. While the definite result of stenting carrying a significantly higher risk than surgery with respect to short-term events cannot be disputed, the differences between the treatments were small and neither procedure has been shown to be risk-free.

The Department of Health, the National Health Service in the United Kingdom and health authorities elsewhere are promoting the participation of patients in the decision-making process (Department of Health 2009) and patients are encouraged to take a more active role in their clinical care. This requires a well-informed patient and informed decisions by patients judged to have the capacity to consent should be respected. This is not limited to the choice of hospital and doctor but extends to having a choice in what treatment they receive, even if that represents an in the eyes of the medical profession 'unwise' choice such as to forego carotid endarterectomy in favour of stenting (or not have invasive treatment at all). In light of these new realities it must be kept in mind that the absolute risk difference between stenting and endarterectomy is small. Moreover, the vast majority of patients will not experience any complications at all. ICSS provided robust data on the risk of stenting for the first time and patients can now be informed about risks of benefits of both carotid endarterectomy and carotid stenting. Patients may well decide that the absolute difference in risk is not large enough to keep them from opting for what on the face of it remains the riskier option.

By no means should stenting be routinely carried out in place of endarterectomy. The author of this thesis argues that there is room for carotid stenting as an alternative treatment. Careful patient selection is paramount in order to avoid strokes caused by unnecessary procedures. The best safe-guard for avoiding unnecessary and potentially dangerous procedures and identifying the patients in need of treatment is a multi-disciplinary team led by a neurologist or physician with a special interest in stroke medicine, a surgeon with experience in carotid surgery and a neuro-radiologist with experience in angiography and stenting. The main point of contact for patients should be the neurologist or physician with a special interest in stroke medicine who is normally not directly involved in the delivery of either treatment and thus has no vested interest and is in a position to advise patients free of bias. This advice should start with pointing out that carotid endarterectomy is the treatment of choice for the treatment of symptomatic carotid artery stenosis. It should also contain reference to stenting and its risks and benefits. Patients not expressing a preference after receiving all relevant information should normally undergo carotid endarterectomy. The decision not to have any invasive treatment should be respected, as should the wish for stenting. A high-class centre specialising in treating patients with carotid stenosis should therefore strive to have carotid stenting in their armoury in order to accommodate patients unwilling or unable to undergo surgery. Almost 2% of the patients allocated to surgery crossed over to stenting in ICSS. The ICSS study population was in a highly selected population thought to be equally suitable for surgery and stenting. The number of patients who turn out not to be suitable for surgery is bound to be higher in the wider population.

It has been suggested that only centres that are able to demonstrate a very low complication rate should be allowed to carry out stenting. However, it is unlikely that any individual centre will be able to achieve sufficient numbers to provide this data. After all, ICSS required 1700 patients to show a statistically significant difference between treatments. Moreover, the ICSS centres with a high caseload were no better than the overall ICSS result despite their claims that this was the case (author's unpublished

observation). It may be argued that none of the investigators in ICSS had sufficient experience. Suggested requirements to achieve technical competence to perform carotid artery stenting range from ten supervised carotid stenting procedures to at least 75 supervised carotid stenting procedures with a minimum of 50 procedures per year to maintain competence (Barr *et al.* 2003; Rosenfield *et al.* 2005; Cremonesi *et al.* 2006). It has been suggested that it may take active carotid artery stenting units up to 2 years before the stroke/death rates fall below 5% (Smout *et al.*). It is questionable that prospective stenters should practise on patients to gain the necessary experience when surgeons achieve better results with less experience.

### 13.4 Scope for Further Research

The need for careful patient selection has been emphasised. Currently, the decisions to treat are based on rather crude instruments. The main points taken into consideration are the time since symptoms and the degree of stenosis. Evidence from coronary artery disease and carotid research suggests that the risk of stroke associated with carotid disease is determined by more than just the degree of stenosis. This presents an avenue for future research and researchers have been successful in linking plaque pathology and stroke. Jonathan Gillard's group in Cambridge have contributed a large body of work using various imaging modalities of carotid plaque (U-King-Im *et al.* 2004; Tang *et al.* 2008; U-King-Im *et al.* 2008; Patterson *et al.* 2009; Sadat *et al.* 2009; Tang *et al.* 2009). Their work adds to findings of other investigators that different plaque components contribute to the plaque's stability, correspond to histological findings and are associated with stroke (Spagnoli *et al.* 2004; Ouhlous *et al.* 2005; Clarke *et al.* 2006; Redgrave *et al.* 2006).

Researchers are only in recent years beginning to understand the significance of very small areas of bleeding in the brain that can be picked up by special MRI techniques (microbleeds). They are thought to be associated with stroke (Werring *et al.* 2004; Werring *et al.* 2005; Werring 2007; Gregoire *et al.* 2010) and may increase the procedural risk of stenting and carotid endarterectomy. Further research in this field may help to improve the safety of invasive carotid treatment.

Improving the safety of carotid endarterectomy and stenting is only one side of the medal, though. Given that carotid endarterectomy was established as the treatment of choice at a time when medical treatment of cerebrovascular risk factors was still in its infancy, the question if invasive treatment is superior to current medical therapy at all remains. An exploratory study has been set up to compare carotid endarterectomy to modern conservative medical therapy of carotid stenosis and should shed light on this question.

While extensive research has been carried out in the field of carotid artery stenosis, many questions surrounding prevention of stroke and treatment of carotid artery stenosis remain to be answered and many avenues for future research still exist.

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## Appendix I – CAVATAS collaborators

Centres randomising patients with carotid stenosis between surgery and endovascular treatment and individual investigators. Centres marked with an asterisk (\*) also randomised patients between endovascular treatment and medical care in CAVATAS-MED.

### *Australia*

**\*Austin and Repatriation Medical Centre**, Heidelberg: CF Bladin, GA Donnan, G Fell, G Fitt, J Royle

**Royal Melbourne Hospital**: S Davis, R Gerraty, P Mitchell

**\*Royal Perth Hospital**: MA Goodman, GJ Hankey, MS Khangure, MM Lawrence-Brown, J Linto, W McAuliffe, FJ Prendergast, K Siennarine, EG Stewart-Wynne

### *Canada*

**\*Ottawa General Hospital**: S Grahovac, W Morrish, N Pageau, CE Pringle, DM Richard

### *Finland*

**\*Kuopio University Hospital**: H Manninen, J Sivenius, T Saari

### *Germany*

**Heinrich Heine University**, Düsseldorf: J Malms, L Reiher, M Siebler

### *Italy*

**\*Policlinico St Marco**, Bergamo-Zingonia: G Belloni, M Porta

### *Spain*

**\*Hospital Clinic I Provincial**, Barcelona: A Chamorro, N Vila, V Rimbau, F Vazquez

**Hospital Universitario Virgen del Rocío**, Sevilla: F Boza, JL Garcia Rodríguez, A Gil Peralta, A González, JR González Marcos, A Mayol Deya J Rauno

### *Switzerland*

**\*University Hospital**, Basel: EC Kirsch, PA Lyrer, JA Rem

**Centre Hospitalier Universitaire Vaudois**, Lausanne: J Bogousslavsky, A Uske

*United Kingdom*

**\*Royal Hallamshire and Northern General Hospitals**, Sheffield: JD Beard, TJ Cleveland, C Doyle, PA Gaines, A Sivaguru, GS Venables

**\*Atkinson Morley's and St George's Hospitals**, London: MM Brown, T Buckenham, A Clifton, D Colquhoun, F Crawley, PW Leopold, T Loosemore, DJH McCabe, A Pereira, J Rogers, R S Taylor

**\*The Walton Centre**, Liverpool: TP Enevoldson, G Gilling-Smith, P Harris, T Nixon

**King's College**, London: P Baskerville, T Cox, S Fraser, M Jeffrey, H Markus, J Molloy

**Royal London**, London: P Butler, J Dick, F Frankel

**\*Western General Hospital**, Edinburgh: A Bradbury, D Collie, JA Murie, CV Ruckley, PAG Sandercock, D Schultz, R J Sellar, J Wardlaw

**Withington Hospital**, Manchester: RJ Ashleigh, CN McCollum, P O'Neill

**Newcastle General Hospital**: A Gholkar, AD Mendelow, TJ Walls

**University Hospital of Wales**, Cardiff: H Angus-Leppan, S Halpin, J Hughes, I Lane, M Wiles, AM Wood

**Gloucestershire Royal Hospital**: PA Birch, JJ Earnshaw, GN Fuller, B Heather, K Poskitt, AJ Tottle

**\*Queen's Medical Centre**, Nottingham: DT Hope, D Jefferson, N McConachie

**Queen Elizabeth Neuroscience Centre**, Birmingham: M Duddy, MTE Heafield, RK Vohra



## Appendix 2 – The Carotid and Vertebral Artery Transluminal Angioplasty Study Protocol<sup>1</sup>

### Protocol Summary

**Introduction:** One of the major preventable causes of stroke is thromboembolism from stenosis of the carotid or vertebral arteries. Clinical trials have shown that carotid surgery is a benefit in preventing further strokes in patients with recently symptomatic severe carotid stenosis. However, surgery also carries a significant morbidity. Percutaneous transluminal angioplasty (PTA) has become an established treatment for coronary and peripheral vascular disease. Preliminary results suggest that PTA of carotid and vertebral stenosis also has an acceptable complication rate and may provide an alternative to surgery. PTA typically requires only a short hospital stay and has the advantage of avoiding the risks of general anaesthesia as well as the discomfort and cost of surgery. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) is an international multicentre randomised trial, which has been established to evaluate angioplasty in patients with cerebrovascular disease.

- Aims:
- 1) To determine the risks and benefits of carotid and vertebral angioplasty.
  - 2) To compare the risks and benefits of carotid and vertebral angioplasty with surgical treatment in patients who are eligible for surgery or best medical treatment alone in patients ineligible for surgery.

**Centre Requirements:** A neurologist with an interest in cerebrovascular diseases; a vascular surgeon or neurosurgeon with expertise in carotid endarterectomy; a radiologist with training in neuroradiology and the techniques of angioplasty. (Prior experience of carotid or vertebral angioplasty is not required as this will be an entirely new procedure at most centres)

**Inclusion Criteria:** Stenosis of the internal or common carotid or vertebral artery suitable for percutaneous transluminal balloon dilation and/or stenting. Patients also suitable for surgery are randomised between angioplasty and surgery. Patients unsuitable for surgery are randomised between percutaneous transluminal techniques and medical

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<sup>1</sup> The CAVATAS protocol (September 1996) is reproduced in an abridged version in this thesis.

treatment alone. All patients have the best medical treatment, whatever their randomisation group. The majority of patients should have relevant symptoms with six months but asymptomatic patients may be randomised if treatment is considered appropriate.

**Grey Area:** Individual centres need only randomise patients in their own "grey area" eg an individual centre might only randomise patients not fit for surgery between angioplasty and medical treatment, or only patients with vertebral artery stenosis.

**Randomisation:** Randomisation is by a simple telephone call to the randomisation centre at the Clinical Trials Unit, Oxford. Randomisation is stratified within each centre and balanced within the treatment groups.

**Angioplasty Protocol:** Angioplasty will be carried out by percutaneous transluminal interventional techniques, including the use of balloon dilation catheters and/or stents. Patients will be pre treated with an antiplatelet agent and anticoagulated with heparin during the procedure and for a minimum of 24 hours afterwards. An antiplatelet agent will be continued throughout the follow up.

**Follow-up:** Patients will be followed up at one month, six months and then at yearly intervals to determine the incidence of stroke and death. Where possible, patients will be followed up using ultrasound and/or angiography to determine the rate of restenosis.

**Trial Organisation:** The trial is organised on behalf of the collaborators by the central office at St George's Hospital Medical School, University of London. A distinguished monitoring committee have been established.

**Funding:** The British Heart Foundation has supported the initial period of the study. From June 1994 CAVATAS will be funded for a period of 3 years by the National Health Service Executive Research & Development Programme on Cardiovascular Disease and Stroke.

## Background

**Carotid artery stenosis and stroke:** Stroke is an important cause of death and disability. Considerable effort has therefore been focused on identifying the causes of stroke with a view to preventive treatment. Atheromatous disease of the carotid and vertebral arteries is an important cause of ischaemic strokes, most of which result from embolism of thrombus formed on ulcers or stenosis to more distal branches. The mechanisms involved in thrombus formation at these sites are uncertain, but the risks are partly proportional to the degree of stenosis, the presence of ulceration and possibly the occurrence of haemorrhage within the atheromatous plaque.<sup>1</sup> A smaller proportion of strokes may result from haemodynamic ischaemia distal to severe arterial stenosis or occlusion. In younger patients other causes of arterial stenosis, such as fibromuscular dysplasia or dissection may be relevant.

Many strokes occur unheralded, but about 20% are preceded by transient ischaemic attacks (TIA) or minor strokes which recover without significant disability. These events provide the opportunity for therapeutic intervention if stenosis is detected, to prevent a further catastrophic major stroke. The risk of stroke following a TIA is about 8% in the first year and then 5% per annum,<sup>2</sup> but in patients with severe carotid stenosis the risk in medically treated patients increases to as high as 28% over 2 years<sup>3</sup>.

There is a strong association between carotid atherosclerosis and cardiovascular disease, particularly coronary heart disease<sup>4</sup>. Asymptomatic carotid stenosis may therefore also be detected during the course of routine screening of patients with ischaemic heart disease or peripheral vascular disease. The risks of stroke occurring in patients with carotid stenosis who have not had previous cerebrovascular symptoms are lower than patients who have had TIAs, other things being equal. In one study the annual risk of stroke in asymptomatic patients with severe carotid stenosis was 3.4%<sup>5</sup>. The published trials have not lent strong support to the policy of routine carotid surgery for asymptomatic stenosis<sup>6,7</sup>. Prophylactic surgical treatment is therefore not usually recommended in asymptomatic patients, at least in Europe, although the results of the ongoing asymptomatic carotid surgery trials in progress are awaited with interest. However, in patients with severe asymptomatic carotid stenosis, major surgery such as coronary artery bypass grafting, increases the risks of stroke at the time of surgery up to four times normal<sup>8</sup>. Treatment of severe asymptomatic carotid stenosis to reduce the risk of stroke can therefore be justified prior to coronary artery bypass or other major surgery.

**Conventional treatment of carotid artery stenosis:** The optimum treatment of carotid artery stenosis is uncertain. Aspirin therapy is of undoubted benefit in patients who have had TIAs, but at best only prevents 25% of embolic strokes that would otherwise have

occurred and cannot be expected to prevent haemodynamic stroke<sup>9</sup>. Anticoagulation has not been shown to be of any greater benefit. Consequently, a considerable portion of strokes cannot be prevented by current medical treatment. Carotid endarterectomy therefore continues to be considered as an addition to medical therapy, with the aim of removing atheromatous sources of thrombo-embolism and/or improving cerebral perfusion pressure. Until recently the value of carotid endarterectomy was disputed, because of concern about the risks of the procedure<sup>10,11</sup>. The reported rate of death or major stroke following carotid endarterectomy in earlier studies varied from 2% to 21%,<sup>12,13</sup> with an average combined mortality and stroke risk estimated at around 6%<sup>14</sup>. However, the recent results of the European Carotid Surgery Trial (ECST)<sup>15</sup> and the North American Symptomatic Carotid Endarterectomy Trial (NASCET)<sup>3</sup> have convincingly demonstrated the benefits of carotid endarterectomy in preventing stroke in medically fit patients with carotid stenosis of greater than 70%. The ECST also showed that surgery confers no significant benefit if the stenosis is less than 30%, but the value of surgery remains uncertain in patients with stenosis of between 30 and 69%. Despite the overall benefits of carotid endarterectomy in the ECST there was still a significant risk of stroke or death resulting from surgery of 7.5%. Carotid endarterectomy also risks significant morbidity from myocardial infarction, particularly in patients who have ischaemic heart disease or severe hypertension<sup>16</sup>. There are also anaesthetic hazards, such as pulmonary embolism, and minor morbidity from the surgical incision, such as cranial nerve palsy<sup>13</sup>. A disadvantage of surgery in the UK is that treatment may be delayed by several weeks, during which time a devastating stroke may occur.

**Vertebral artery stenosis and stroke:** A significant percentage of strokes within the vertebro-basilar territory result from vertebral artery stenosis or occlusion. Surgery is rarely considered for vertebral artery disease because of its technical difficulty, but some cases appear to be ideal candidates for PTA<sup>17</sup>. The natural history of vertebral artery stenosis and the value of PTA at this site are uncertain and therefore warrant further study.

**Percutaneous angioplasty:** Following the introduction of percutaneous transluminal angioplasty (PTA) by Dotter and Judkins in 1964, PTA has become established in the treatment of peripheral, renal and coronary vascular disease. The success rate in these situations approaches 90%, with serious complications occurring in less than 5% of procedures<sup>18,19</sup>. PTA has the advantage that the procedure is brief, does not require a surgical incision and can be performed under local anaesthesia. It was therefore logical to extend the procedure to the carotid arteries, but initially this was not recommended because of anxiety about the risks of cerebral embolism resulting from the procedure<sup>19,20</sup>. However, reports appeared of successful dilation of common carotid stenosis through an

arteriotomy<sup>21</sup> and then by PTA<sup>22</sup>. Fibromuscular dysplasia of the internal carotid artery and of other brachiocephalic arteries was also successfully treated by PTA<sup>22-26</sup>. With increasing experience, several case reports and series of PTA for atherosclerotic stenosis of the internal carotid have appeared, suggesting that the procedure might be safer than previously suggested (see Table). By 1995 a total of 447 patients with atherosclerotic internal carotid stenosis and a smaller number with vertebral artery stenosis treated by PTA have been reported, with an observed stroke rate associated with the procedure of less than 5%<sup>27-41</sup>. The precise risks of the carotid PTA are as yet undefined, but this preliminary experience suggests that the risks of stroke are comparable to those of carotid endarterectomy.

**Potential hazards of PTA:**

- Cerebral embolism due to dislodgement of atheromatous material or thrombus from the vessel wall is the most serious risk of PTA. The risk of embolisation may be reduced by avoiding patients with angiographic evidence of thrombus within the artery, by pre-treatment with Aspirin and by anticoagulation at the time of the procedure. Embolism or occlusion may also occur from thrombus formed on the damaged intima after PTA. Anticoagulation and/or antiplatelet agents should therefore be continued after the procedure.
- Haemodynamic cerebral ischaemia may occur during the temporary occlusion of the internal carotid artery by the inflated balloon. Cerebral damage from haemodynamic ischaemia can be avoided by limiting the period of balloon inflation to a maximum of 40 seconds. In selected cases, the fall in perfusion pressure can be minimised by injecting oxygenated arterial blood through the lumen of the catheter during balloon inflation.
- Contrast reactions.
- Haemorrhage and/or pseudo-aneurysm formation at the arterial puncture site.
- Reflex bradycardia and hypotension may result from the inflation of the balloon in the region of the carotid sinus. This can be controlled by Atropine therapy.
- A reflex local arterial spasm may occasionally be induced by stretching the carotid artery. This can be controlled by a local infusion of an appropriate pharmacological agent.
- Transient neck pain and ipsilateral frontal headache occur occasionally and may be the result of stretching of the carotid artery.

- Arterial rupture may occur. This is very uncommon.

The mechanism by which PTA results in an increase in vessel diameter involves the development of splits in the intima and plaque, and sometimes in the underlying media. Arterial dissection in some cases is therefore an inevitable consequence of successful PTA, but is usually limited to the area of balloon dilation.

Restenosis is a well-recognised disadvantage of PTA at other sites where symptoms such as angina are caused by a reduction in flow. However, restenosis may not be so disadvantageous after carotid or vertebral PTA unless it leads to emboli or complete occlusion. The preliminary results of carotid PTA suggest patency rates at 1 year of around 84%.<sup>35</sup> Restenosis may possibly be prevented by the use of antiplatelet agents.

**Table summarising known risks of angioplasty for atheromatous carotid artery stenosis**

|   | <u>N</u> | <u>Minor non-disabling Stroke</u> | <u>Major Stroke</u> |
|---|----------|-----------------------------------|---------------------|
| Bockenheimer & Mathias 1983 <sup>27</sup> | 3        | 0                                 | 0                   |
| Wiggli & Gratzl 1983 <sup>28</sup>        | 2        | 0                                 | 0                   |
| Tsai et al 1986 <sup>29</sup>             | 6        | 0                                 | 0                   |
| Freitag et al 1987 <sup>31</sup>          | 11       | 0                                 | 0                   |
| Theron et al 1990 <sup>33</sup>           | 13       | 0                                 | 0                   |
| Kachel et al 1991 <sup>34</sup>           | 37       | 0                                 | 0                   |
| Munari et al 1992 <sup>35</sup>           | 44       | 3                                 | 1                   |
| Eckert et al 1994 <sup>36</sup>           | 53       | 0                                 | 1                   |
| Mathias 1994 <sup>37</sup>                | 166      | 1                                 |                     |
| Gil-Peralta 1995 <sup>38</sup>            | 62       | 0                                 | 3                   |
| Brown et al 1995 <sup>39</sup>            | 50       | 1                                 | 2                   |
| TOTAL                                     | 447      | 5<br>(1.1%)                       | 10<br>(2.2%)        |

**Trial proposal:** The preliminary experience suggests that PTA of the carotid and vertebral arteries is technically feasible and has considerable advantages over endarterectomy in terms of avoiding the risks of general anaesthesia and surgical incision. The incidence of cerebral embolism seems in the small series to date comparable with that of carotid endarterectomy and possibly better. PTA also has major advantages over endarterectomy in terms of resource allocation and patient comfort. The procedure

is technically simple and there is immediate ascertainment of any neurological complications since the patient remains conscious throughout. In addition, PTA provides an option for the treatment of patients who are not fit for surgery.

Encouraged by these preliminary results, a formal international multi centre scientific prospective randomised trial of carotid and vertebral artery percutaneous transluminal angioplasty (CAVATAS) has been established with a defined protocol to determine more fully the success rate, risks, benefits, and indications for the procedure. To demonstrate a benefit, careful investigation and selection of patients before the procedure and non-invasive investigation during follow up will be essential. If the low complication rate is confirmed, PTA will provide a valuable new therapy for the management of cerebrovascular disease.

### **Aims of CAVATAS**

1. To determine the risks and benefits of carotid and vertebral angioplasty.
2. To compare the risks and benefits of carotid and vertebral angioplasty with surgical treatment in patients eligible for surgery or best medical treatment alone in patients ineligible for surgery.

### **Secondary aims are:**

1. To evaluate the use of different guide wires, predilation and dilation catheters, including cerebral protection balloons and the use of stents.
2. To identify risk factors for angioplasty and surgery, e.g. calcified plaques.
3. To determine the recurrence rate of stenosis following angioplasty and surgery.

### **Protocol of Investigation**

**Central Office:** The study will be organised on behalf of the collaborators by a central office at St George's Hospital Medical School, University of London. The central office will be responsible for protocol design, data collection and analysis of the results but will consult with the collaborators at the annual investigators meeting and as necessary at other times.

**Participating Centre Requirements:** Patients entered into the study will be seen prior to randomisation and during follow up by a designated neurologist or physician with an interest in cerebrovascular disease. Centres randomising to carotid endarterectomy will have a designated vascular surgeon or neurosurgeon with expertise in carotid endarterectomy, available to assess eligibility and who will personally carry out all the

carotid endarterectomy operations within the study. PTA will be carried out by a designated radiologist of consultant status, who has had training in neuroradiology and the techniques of angioplasty. (Prior experience of cerebrovascular angioplasty is not required as this will be an entirely new procedure at most new centres). Participating centres will be required to submit curriculum vitae of the principal investigators and satisfy the credentials subcommittee that they have appropriate experience and expertise to join the study. New centres will be encouraged to obtain training in cerebrovascular PTA techniques at one of the active CAVATAS centres and will be requested to invite one of the radiologists from an experienced centre to attend the first few PTA procedures at the new centre.

**Inclusion criteria:** Patients will be eligible for inclusion in the study if angiography demonstrates unilateral or bilateral stenosis of the common carotid artery, carotid bifurcation, external carotid artery, internal carotid artery or extracranial vertebral artery considered suitable for percutaneous transluminal balloon dilation and/or stenting.

**Patient groups:** Two groups of patients will be studied and randomised separately:

1. **Patients eligible for surgery:** Patients with carotid or vertebral artery stenosis, which the clinician and the patient would be happy to treat by either surgery or percutaneous transluminal techniques.

Patients eligible for surgery will be randomised in equal numbers to surgery or angioplasty.

2. **Patients ineligible for surgery:** Patients considered inappropriate candidates for surgery with carotid or vertebral stenosis, which the clinician and the patient would be happy to treat by percutaneous transluminal angioplasty or medical treatment.

Patients ineligible for surgery will be randomised in equal numbers to angioplasty or best medical treatment alone.

All the patients randomised to interventional treatment will have the best medical treatment in addition to PTA or surgery, which should include control of hypertension, diabetes and hypercholesterolaemia, and an antiplatelet agent or anticoagulant as appropriate.

**Grey area:** Patients should only be randomised if the investigator is uncertain which of the alternatives is the best treatment for that patient at that time. Individual centres need only randomise patients in their own "grey area". This allows centres to only randomise



patients who they are happy to treat by angioplasty. In an individual centre this might mean only randomising patients who were not fit for surgery between angioplasty and medical treatment or in another centre only vertebral artery disease. Each centre will provide a written policy statement defining their grey area.

**Angiographic features:** Suitability for PTA will be a matter for individual judgement by the collaborating radiologists, but guidelines will be issued during the course of the study if any particularly high risk factors emerge. At least 30% linear diameter stenosis should be present. Stenosis due to atherosclerosis, fibromuscular dysplasia, webs or post surgical fibrosis may be included.

**Eligibility for carotid endarterectomy:**

Severe carotid stenosis: Following the results of the ECST and NASCET otherwise fit patients with appropriate symptoms or signs and 70% or greater carotid stenosis (using the ECST criteria) will normally be randomised between surgery and PTA in group I if an experienced vascular surgeon is available. If no suitable surgeon is available or the patient refuses surgery, then patients with severe stenosis can be randomised between PTA and medical treatment in Group 2.

Moderate carotid stenosis: The benefits of carotid endarterectomy remain uncertain in patients with moderate stenosis of between 30 and 69%. Patients with moderate stenosis considered suitable for surgery can be randomised within CAVATAS between surgery and PTA. If a patient with moderate stenosis is considered ineligible for surgery but the investigator is uncertain whether PTA or medicine alone would be the best treatment for the patient, then the patient should be randomised between PTA and medicine.

**Ineligibility for surgery:** Patients randomised between PTA and medicine may include:

- (a) patients at high risk from surgery because of ischaemic heart disease, poorly controlled hypertension, liver disease, decompensated diabetes mellitus or other medical risk factor.
- (b) patients with anatomical factors making surgery difficult or impossible, such as a high site of carotid stenosis or a rigid neck or inaccessible vertebral artery stenosis.
- (c) patients refusing surgery.

**Symptoms:** It is anticipated that the majority of the patients considered for PTA will have had appropriate cerebrovascular symptoms or signs of embolic and haemodynamic cerebral ischaemia within 6 months of randomisation. However, asymptomatic patients

or patients with more distant symptoms may be randomised if intervention is considered appropriate by the Clinician, e.g. major surgery, such as cardiac bypass, is planned. Patients with recent symptoms will be randomised separately asymptomatic patients.

**Disease of more than one artery:** Patients who, at the time of randomisation, or subsequently, develop indications for treatment of more than one carotid or vertebral artery, may have more than one artery treated if clinically indicated as follows:

**If two or more arteries are suitable for PTA,** the patient should be randomised for the artery, which is to be treated **first**. All the arteries to be treated at the same time or subsequently should then receive the same treatment (PTA, surgery or medical treatment alone) allocated by randomisation.

**If only one artery is suitable for PTA and this artery requires treatment first,** then the patient should be randomised first. After treatment of this artery as randomised, the patient may have surgical treatment of other arteries not suitable for PTA.

**If the artery to be treated first is only suitable for surgery and is not suitable for PTA,** surgery should be carried out first and the patient randomised between PTA and surgery (or medical treatment alone) for the second artery when the patient is fit for the second procedure.

As a general principle, patients can only be randomised in the study once.

**Exclusion criteria:** The following will be absolute exclusion criteria:

1. Unwilling or unable to give informed consent.
2. Thrombus present on preliminary angiography.
3. Major stroke with no useful recovery of function within the territory of the treatable artery.
4. Intracranial stenosis beyond the skull base.
5. Stenosis unsuitable for PTA or stenting.

**Non-randomised patients:** Each centre will provide baseline data and the reason for non-randomisation on all patients who are under the care of a collaborating clinician and receive carotid surgery or PTA outside the trial at that centre

**Consent:** Written witnessed informed consent will be obtained from all patients, who will be given a written explanation of the study and its aims.

**Age range:** Not specified.

**General investigations:** All patients should have routine haematology (FBC, platelets) and biochemical blood tests, (renal function, blood sugar, cholesterol), ECG, chest x ray and cranial CT or MRI scan prior to randomisation. In appropriate symptomatic patients, echocardiography should be performed to detect cardiac sources of emboli.

**Ultrasound Doppler imaging:** Where possible, linear measurements of vessel diameter and peak systolic flow will be recorded and the morphology and degree of calcification of the stenosing atheromatous plaque assessed using ultrasound Doppler imaging prior to randomisation and during follow up to allow the anatomical results and patency rates to be compared.

All patients randomised for accessible carotid stenosis will have ultrasound measurements to assess patency at one year as a minimum and then at yearly intervals if possible. The same standardised ultrasound criteria circulated by the Central Office will be used at all centres to assess the degree of stenosis.

**Cerebrovascular reactivity:** In centres where transcranial Doppler is available, cerebrovascular reactivity may be recorded by measuring the increase in the velocity of blood flow occurring during the inhalation of carbon dioxide in both middle cerebral arteries before and after treatment, but is not essential to the protocol.

**Angiography:** Bilateral selective carotid or vertebral angiography (DSA) will be performed prior to randomisation to confirm the suitability of the lesion for carotid endarterectomy and/or PTA and to detect significant disease distal to the carotid bifurcation or vertebral artery. At least two views of the diseased area should be taken. Angiography will be carried out to assess the success of the PTA at 6 to 12 months after the procedure in selected centres. Individual centres may randomise carotid patients after magnetic resonance angiography (MRA) or intravenous DSA and duplex ultrasound without conventional angiography if both investigations agree by arrangement with the central CAVATAS Office and the centre has been able to demonstrate the accuracy of their ultrasound by audit. Patients randomised to PTA after MRA and ultrasound alone in whom preliminary angiography as part of the PTA procedure demonstrates a lesion unsuitable for PTA may cross over to surgery or medicine as appropriate. If MRA and ultrasound results differ in an individual patient then DSA should be performed prior to randomisation.

**Randomisation:** Patients will be randomised by a telephone call to the randomisation centre at the Clinical Trials Unit, Oxford. The telephone call to the randomisation centre may be made from the angiography suite in appropriate cases if prior consent has been obtained and if it is desired to proceed immediately to PTA at the same session if randomised. Alternatively, the investigators may wish to discuss the angiograms to confirm the appropriateness of the lesion for surgery and/or PTA prior to randomisation, in which case PTA can be carried out at a separate session if so randomised. In any case, the allocated treatment should be instituted as soon as practical after randomisation. Randomisation between the different groups will be balanced within each Centre.

**Angioplasty protocol:** Angioplasty will be carried out using percutaneous transluminal interventional techniques, including the use of balloon dilation and/or stents. Where appropriate cerebral protection catheters may be used at individual centres, but are not required by the protocol. Details of the technique and catheter design will be left to the preference of individual participating radiologists to allow flexibility according to individual preference and variation in arterial anatomy. Stents may be used at the discretion of the individual radiologist. Premedication, atropine and the use of local anaesthetic will be discretionary. As a guide, maximum balloon diameter when inflated should not exceed the estimated normal arterial diameter. Hand held inflation without monitoring of pressure is acceptable. Continuous infusion of oxygenated blood through a central catheter lumen during balloon inflation may be used during the treatment of patients with severe bilateral disease or severely impaired haemodynamic reserve, if measured. The number of balloon inflations will normally be limited to a maximum of 3 and the duration of individual inflation limited to a maximum of 30 seconds, to minimize haemodynamic cerebral ischaemia. Two catheters (the second inserted into the common carotid artery to enable visualisation of the stenosis after angioplasty) may be used.

**Anticoagulation regime:** All patients randomised to PTA will be pre treated with Aspirin (minimum dose 150 mg) or an alternative anti platelet agent if preferred for at least 24 hours prior to PTA. Immediately prior to balloon inflation, the patients will be anti coagulated with intra arterial or intravenous Heparin, 5000 units, (or Warfarin continued if already anti-coagulated). Anti-coagulation will be continued for a minimum of 24 hours after PTA, unless contraindicated. Aspirin or an alternative anti platelet agent will then be continued throughout the period of follow up.

**Monitoring:** During the procedure simple neurological examination will be repeated, as frequently during PTA as practical during the procedure. This can be performed by any trained member of staff, e.g. radiology nurse, and should comprise assessment of at least speech and limb movement. The value of continuous monitoring of cerebral blood flow

in the middle cerebral artery ipsilateral to the procedure using transcranial Doppler sonography will be assessed during the study, but is not essential to the protocol. ECG and BP will also be monitored.

**Follow up:** Patients will be carefully followed up by a neurologist or physician to record the presence of new symptoms and neurological signs at one month after procedure or randomisation if randomised to medical care, and then at six months, one year and then yearly intervals after randomisation for at least 5 years. Follow up CT or MRI should be performed in patients who have new neurological symptoms. In individual centres, ultrasound and/or angiography will be carried out at 12 months after randomisation in all angioplasty patients to assess patency rates. (see above)

**Restenosis:** Restenosis will only be treated by further PTA or surgery if the patient has relevant new symptoms. Asymptomatic restenosis will not be an indication to retreat the lesion as the risk of disabling symptoms after restenosis is unknown.

**Cross-overs:** Patients who have further symptoms after technically successful PTA will have the option of further PTA, anticoagulation or cross over to surgery if significant carotid stenosis is present on further investigation. Cross-overs to surgery and angioplasty will be avoided unless clinically essential. Patients ineligible for surgery allocated to medical treatment, who have further symptoms after randomization will have the option of anticoagulation or cross over to PTA if anticoagulation is not effective, but cross over in this Group will be avoided if possible. Patients in whom PTA fails to dilate the artery for technical reasons will have the option of proceeding to early surgery if appropriate.

**Analysis:** The results in symptomatic patients with carotid and vertebral artery disease will be analysed separately, as will the results in patients eligible or ineligible for surgery. Results will be analysed by decade of severity of stenosis. The following will be analysed both immediately after PTA and during the follow up period:

1. **Risks of PTA:** Complications and neurological symptoms, including TIAs, stroke and death occurring during and within 30 days after the procedure. The primary analysis will assess the rates of ipsilateral disabling stroke or death within 30 days of treatment. Disabling stroke will be defined as "needing help as a result of the stroke from another person to perform everyday activities" lasting for 30 days or more after the onset of stroke.
2. **Clinical Benefits:** Period after randomisation free of disabling stroke or death.

3. **Anatomical Benefits:** Alteration in luminal diameter, blood flow velocity, cerebrovascular reactivity, flow characteristics and plaque morphology, where measured.
4. **Statistical Analysis:** The main statistical comparisons will be made between the primary event rates of disabling stroke and/or death in patients randomised to surgery, PTA or medical treatment alone. Sub group analysis will compare patients eligible with those ineligible for surgery, recently symptomatic and asymptomatic (or distantly symptomatic) patients and different degrees of stenosis.

Analysis of crossovers will be by intention to treat. A separate efficacy analysis will be carried out on patients who have had successful angioplasty.

**Recruitment Numbers:** The study plans to recruit a total of 400 symptomatic patients with carotid artery disease (approximately 200 of whom should have received PTA). An analysis will be published at this stage. At current recruitment rates we predict that recruitment of 400 patients will have been achieved by the summer of 1997.

**Monitoring Committee:** The Monitoring Committee will assess the progress of the study at regular intervals and consist of an independent neurologist, medical statistician and one other member. During the period of intake to the study, interim analyses of mortality and of any other information that is available on major endpoints (including serious adverse events believed to be due to treatment) will be supplied, in strict confidence, to the chairman of the Data Monitoring Committee, along with any other analyses that the Committee may request. In the light of these analyses, the Data Monitoring Committee will advise the chairman of the Steering Committee if, in their view, the randomised comparisons in CAVATAS have provided **both** (i) "proof beyond reasonable doubt" that for all, or for some, specific types of patients, one particular treatment is clearly indicated or clearly contraindicated in terms of a net difference in outcome, **and** (ii) evidence that might reasonably be expected to influence materially patient management. Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least 3 standard deviations in an interim analysis of a major endpoint may be needed to justify halting, or modifying, the study prematurely. This criterion has the practical advantage that the exact number of interim analyses is of little importance, and so no fixed schedule is proposed.

**Publication:** Individual participating centres may report their own technical experience of angioplasty during the study, but should not identify individual patients randomised in CAVATAS and should not make direct comparison with the results in patients

randomised to surgery or medicine. Copies of any abstracts or articles including data from patients in CAVATAS should be sent to the Central Office. Publication of the results of CAVATAS will be prepared by the Central Office and circulated to participating centres for comment prior to submission of the manuscript for publication under the authorship of all the CAVATAS collaborators.

**Funding:** The British Heart Foundation has supported the initial period of the study. From June 1994 CAVATAS will be funded for a period of 3 years by the National Health Service Executive Research & Development Programme on Cardiovascular Disease and Stroke.

**Ethical Committee Approval and Indemnity:**

Individual centres are expected to obtain local ethical committee approval for the study. If the local ethics committee approves the study and the patient agrees to enter the study after reading the patient information sheet (which explains the risk of stroke) and signs the consent form, then the study in the United Kingdom should be protected by the National Health Service indemnity which should defend the collaborators against allegations of negligence. In overseas centres it is hoped that a collaborator's own malpractice insurance policy, or that of his institution, would provide cover on the same basis. We are not able to provide no fault compensation for a patient who has a stroke or other mishap as a result of angioplasty or surgery in the trial as we believe that such events are equally likely to happen to eligible patients if they are treated outside the trial.

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## Appendix 3 – Cochrane Search Strategy

1. carotid artery diseases/ or carotid artery thrombosis/ or carotid stenosis/
2. carotid arteries/ or carotid artery, common/ or carotid artery, external/ or carotid artery, internal/
3. constriction, pathologic/
4. 2 and 3
5. (carotid adj5 (stenosis or thrombo\$ or disease\$ or narrow\$ or plaque\$ or arterioscler\$ or atheroscler\$)).tw.
6. 1 or 4 or 5
7. angioplasty/ or angioplasty, balloon/ or angioplasty, balloon, Laser-assisted/
8. Balloon Dilatation/
9. Stents/
10. (angioplasty or stent\$ or endovascular).tw.
11. (balloon adj5 (dilat\$ or catheter\$)).tw.
12. ((endoluminal or transluminal) adj5 repair\$).tw.
13. 7 or 8 or 9 or 10 or 11 or 12
14. 6 and 13
15. Randomized Controlled Trials/
16. random allocation/
17. Controlled Clinical Trials/
18. control groups/
19. clinical trials/ or clinical trials, phase i/ or clinical trials, phase ii/ or clinical trials, phase iv/
20. double-blind method/
21. single-blind method/
22. Therapies, Investigations/
23. Research Design/
24. Randomized controlled trial.pt.

25. Controlled clinical trial.pt.
26. clinical trial.pt
27. random\$.tw.
28. (controlled adj5 (trial\$ or stud\$)).tw.
29. (clinical\$ adj5 trial\$).tw
30. ((control or treatment or experiment\$ or intervention or surgical) adj5 (group\$ or subject\$ or patient\$)).tw.
31. (quasi-random\$ or quasi random\$ or pseudo-random\$ or pseudo random\$).tw.
32. ((control or experiment\$ or conservative) adj5 (treatment or therapy or procedure or manage\$)).tw.
33. (singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$).tw.
34. (coin adj5 (flip or flipped or toss\$)).tw.
35. latin square.tw.
36. versus.tw.
37. controls.tw.
38. or/15-37
39. 14 and 38
40. limit 39 to humans

## Appendix 3 – Odds Ratios for the Outcome Measures Chosen In the Cochrane Review Calculated With the Random Effects Model

The ends of the lines are the 95% confidence intervals (CI). The analyses are based on published results. The large diamond represents the odds ratio and 95% CI of the combined data. The summary estimate statistic is calculated using a Mantel-Haenszel random effects model, the centre of the diamond is the point estimate and its width the 95% CI. The  $\chi^2$  test indicates the strength of evidence for heterogeneity. N is the total number of patients in each treatment group and n is the number of outcome events. Df indicates the degrees of freedom.

**Figure 14.1 – Cochrane Review: Meta-analysis of death or any stroke within 30 days after treatment (random effects model)**

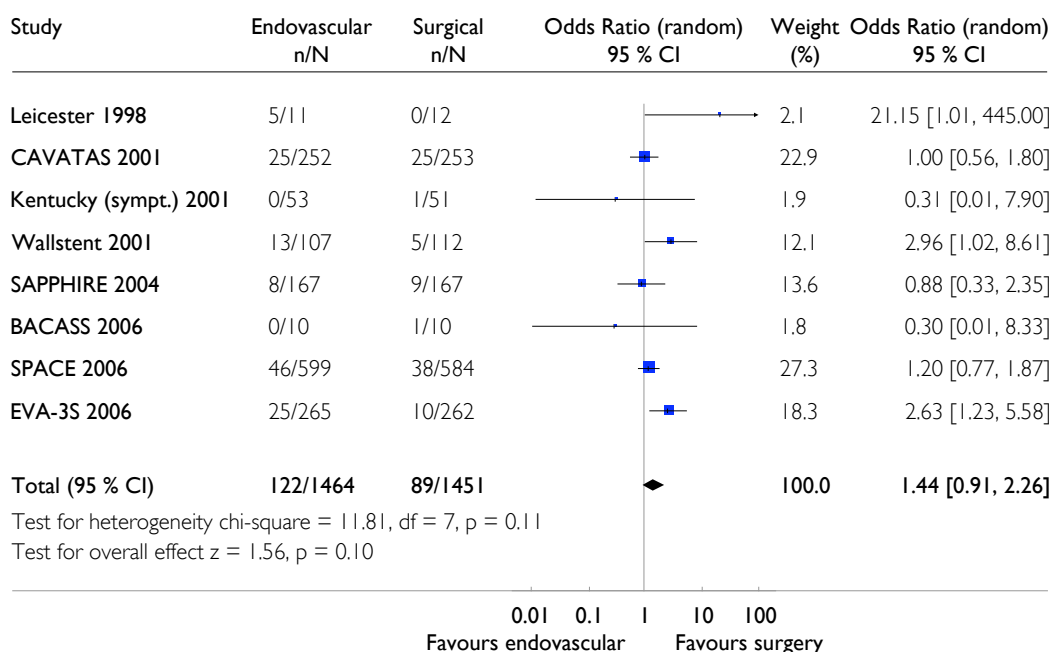


Figure 14.2 – Cochrane Review: Meta-analysis of disabling stroke or death within 30 days after treatment (random effects model)

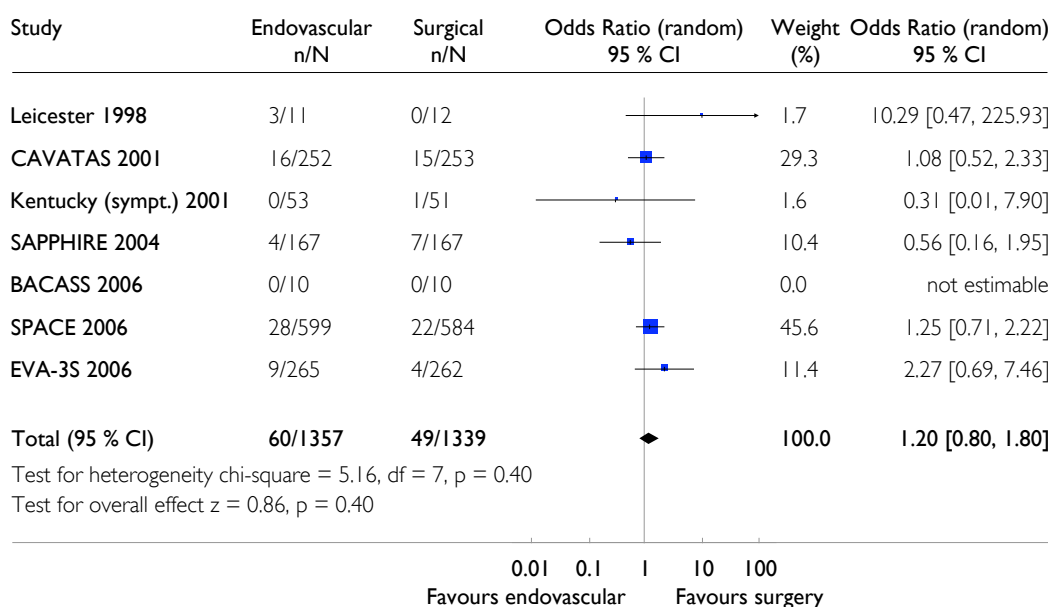


Figure 14.3 – Cochrane Review: Meta-analysis of death within 30 days after treatment (random effects model)

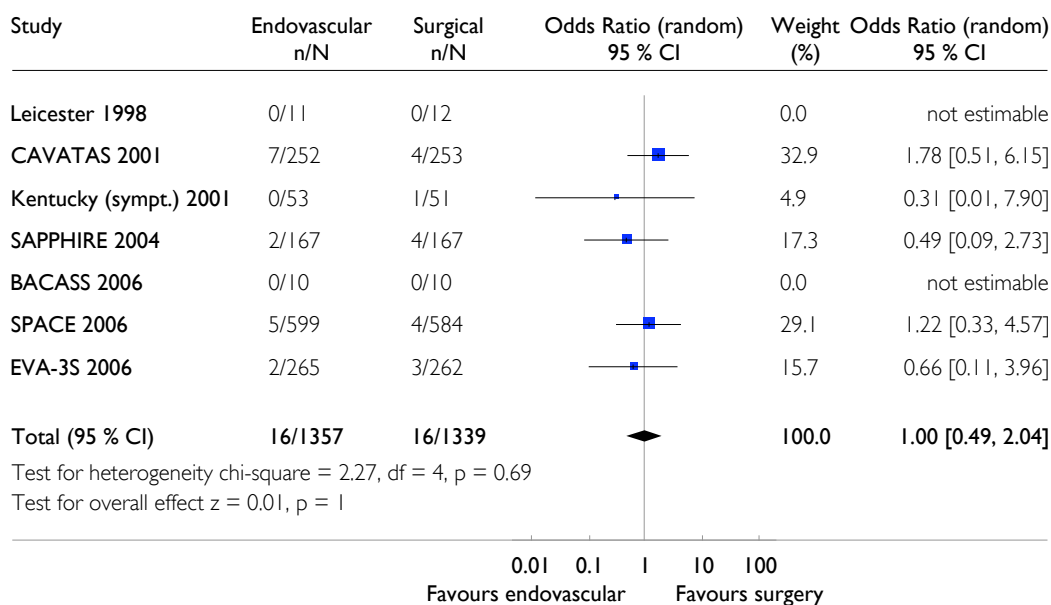


Figure 14.4 – Meta-analysis of stroke within 30 day after treatment (random effects model)

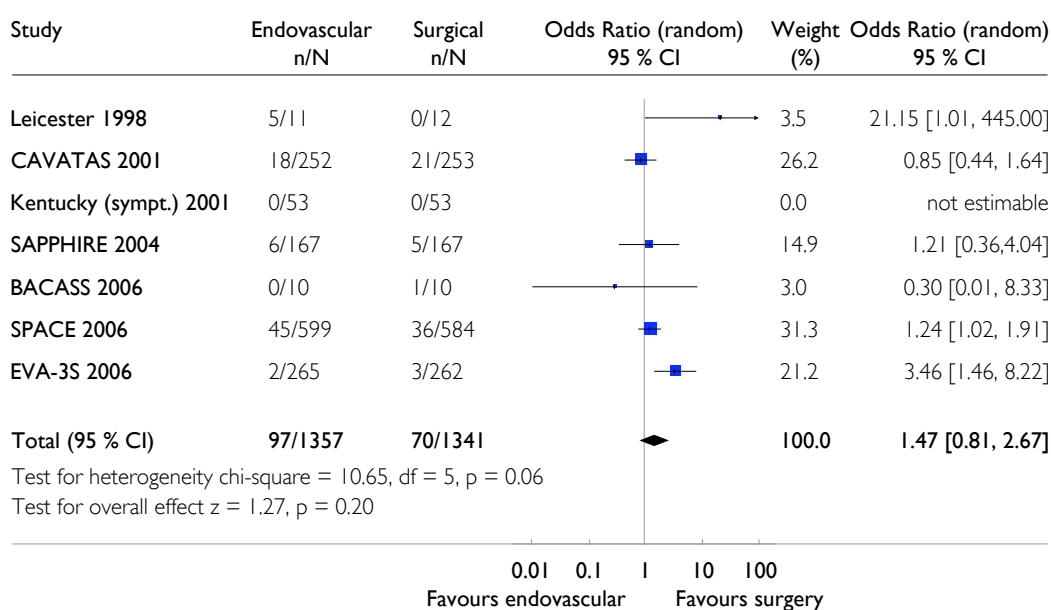


Figure 14.5 – Cochrane Review: Meta-analysis of cranial neuropathy within 30 days after treatment (random effects model)

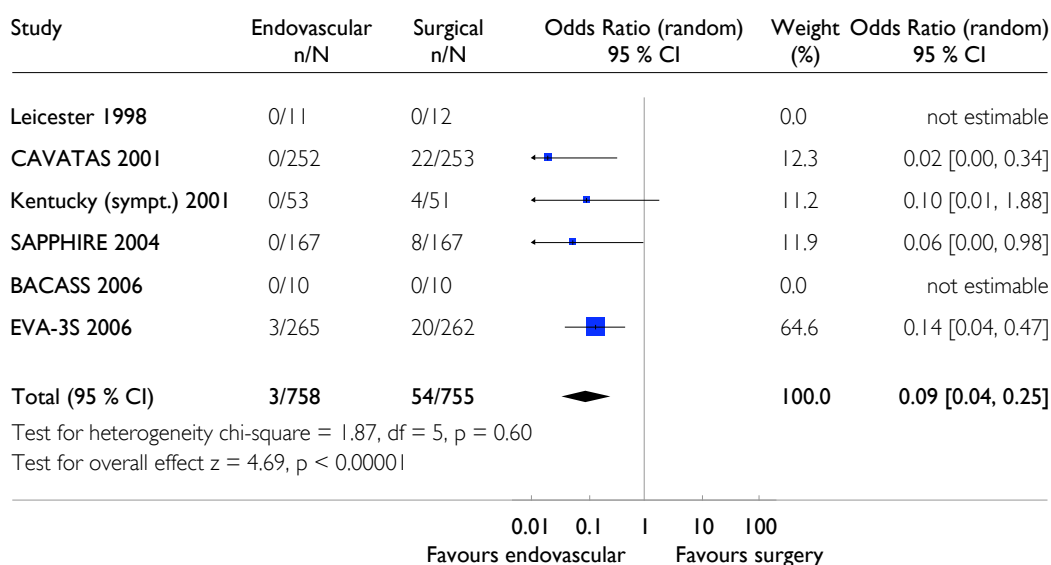




Figure 14.6 – Cochrane Review: Meta-analysis of death or neurological complications within 30 days after treatment (random effects model)

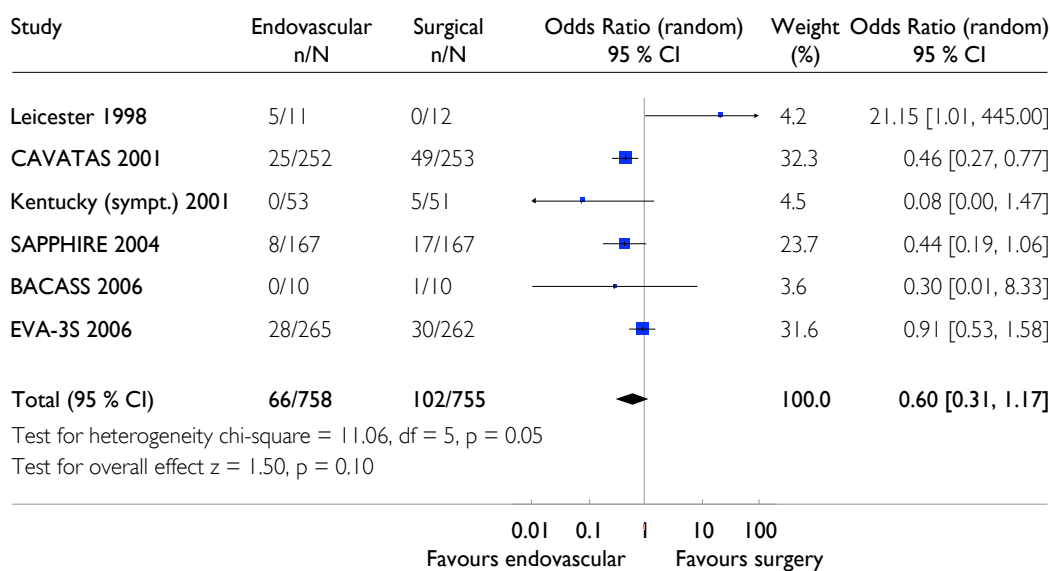


Figure 14.7 – Cochrane Review: Meta-analysis of death or stroke or myocardial infarction within 30 days after treatment (random effects model)

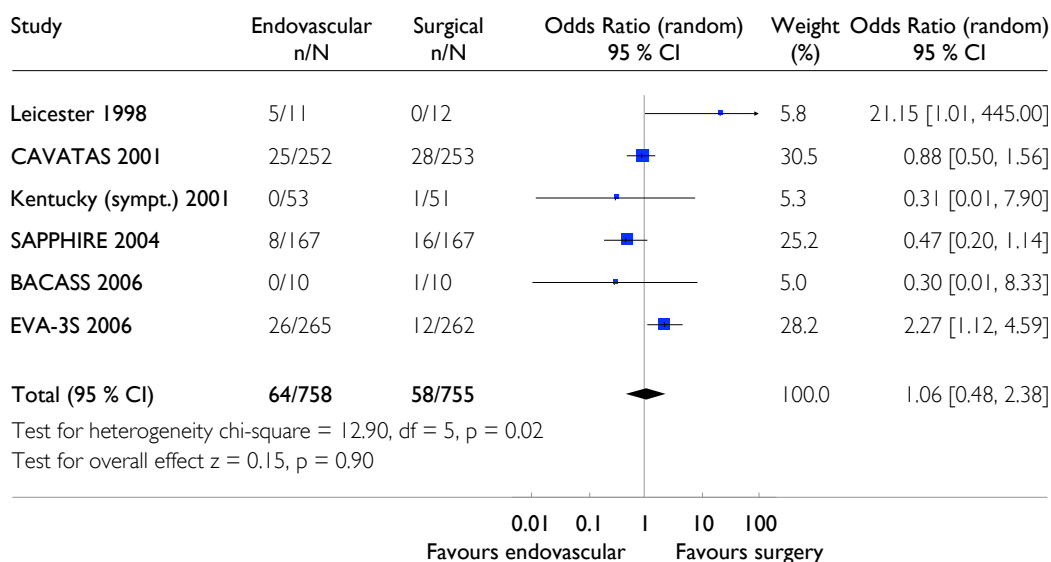


Figure 14.8 – Cochrane Review: Meta-analysis of death, stroke, cranial neuropathy or myocardial infarction within 30 days after treatment (random effects model)

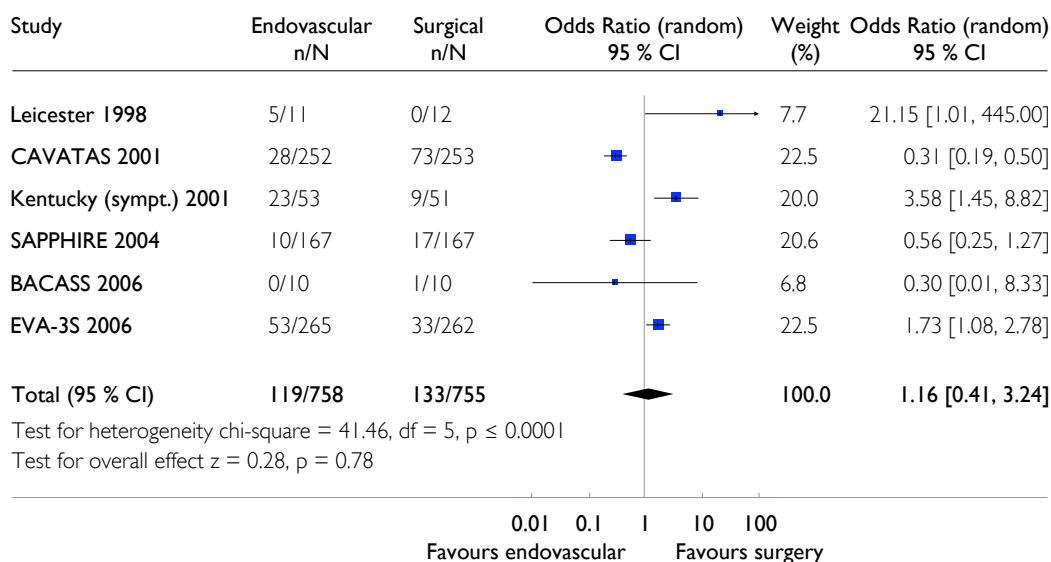


Figure 14.9 – Cochrane Review: Meta-analysis of death or stroke during follow-up (random effects model)

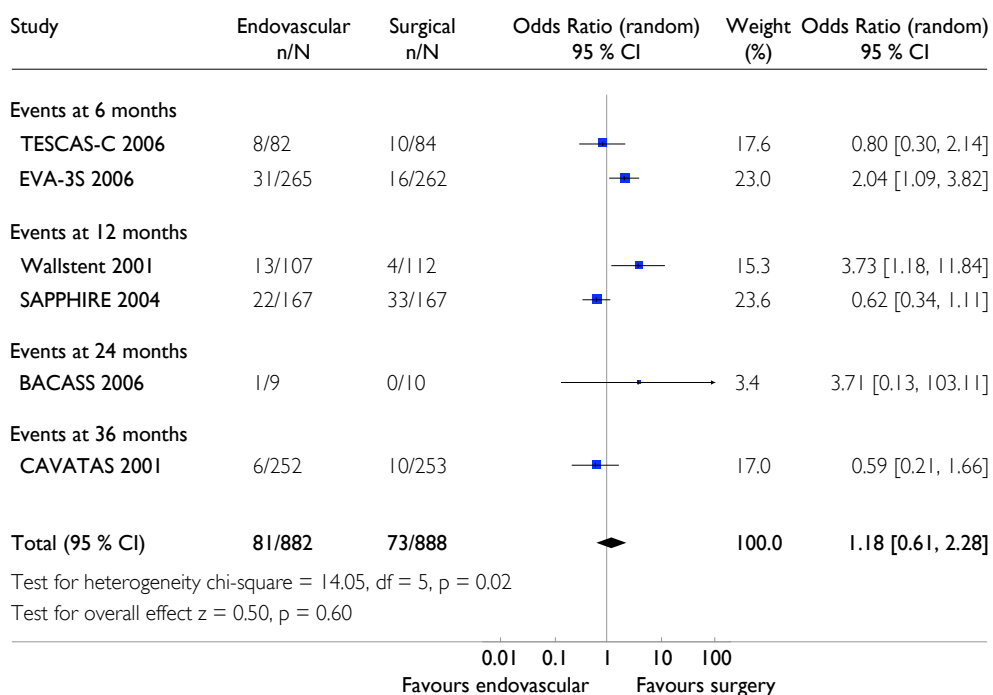


Figure 14.10 – Cochrane Review: Meta-analysis of death occurring more than 30 days after treatment (random effects model)

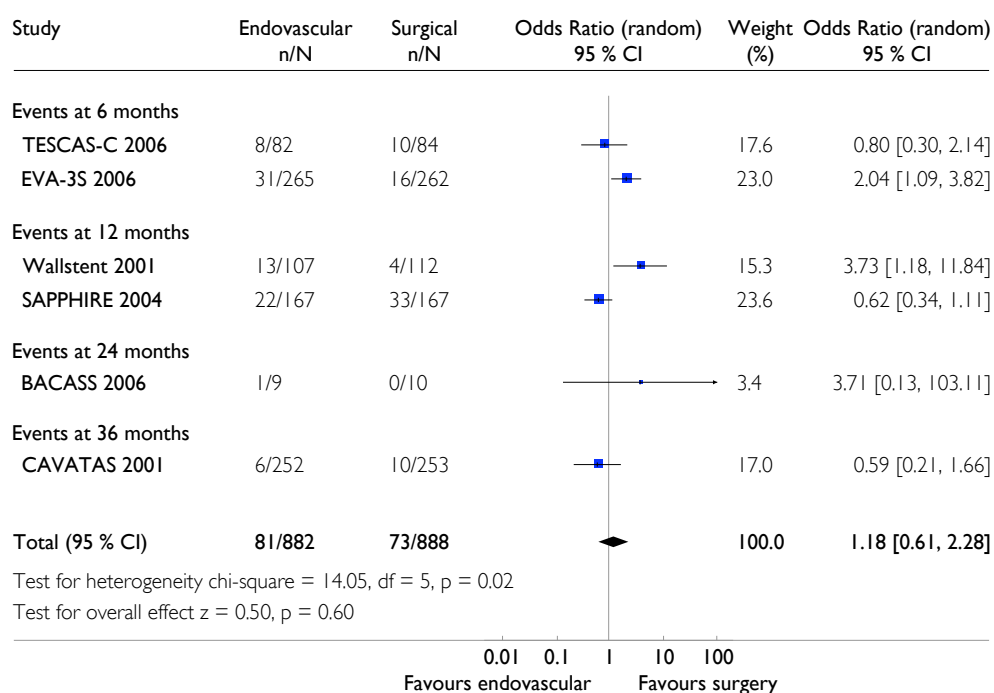


Figure 14.11 – Cochrane Review: Meta-analysis of stroke occurring more than 30 days after treatment (random effects model)

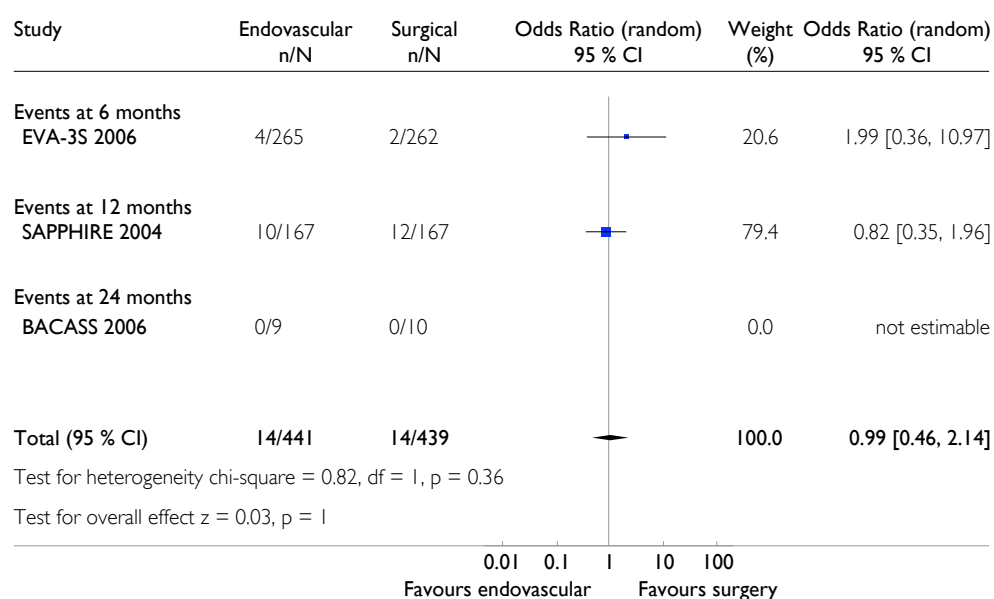


Figure 14.12 – Cochrane Review: Meta-analysis of protected versus unprotected endovascular treatment (random effects model)

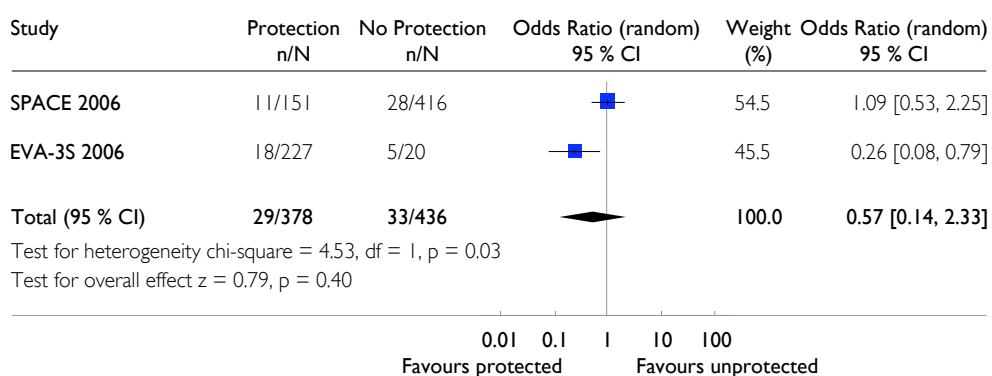
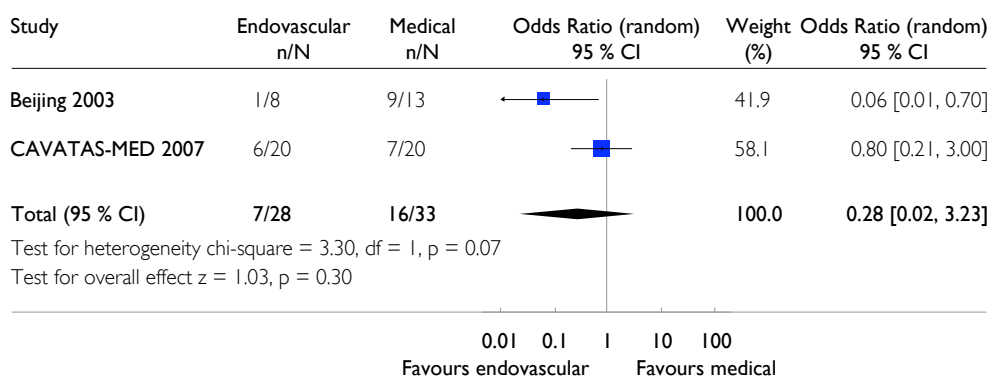


Figure 14.13 – Cochrane Review: Death or stroke occurring more than 30 days after endovascular treatment or randomisation (random effects model)



## Appendix 5 – ICSS collaborators

Centres randomising patients with carotid stenosis between surgery and stenting and individual investigators. Numbers in square brackets are patients randomised

### *Australia*

**Box Hill Hospital (Monash University)**, Melbourne [25]: C Bladin (Neurologist), Dr B Beiles, Dr G Fell, M Grigg (Surgeons), C Clifford (Surgeon and Interventionist), G New (Interventionist)

**Monash Medical Centre**, Clayton [26]: PG Than, S Bower (Neurologists), M Holt, W Chong (Interventionists), R Bell, A Saunder (Surgeons)

**Repatriation General Hospital**, Daw Park, Adelaide [6]: D Schultz (Neurologist), B Stanley, R Scroop (Interventionist), B Stanley (Surgeon and Interventionist), R Foreman (Surgeon)

**Austin Health**, Heidelberg [46]: B Chambers, G Donnan, H Dewey (Neurologists) M Brooks, D Clark, M Molan (Interventionists), N Roberts (Surgeon and Interventionists), A Chan, M Hoare, G Fell, A Roberts, P Chu (Surgeons)

**The Royal Hobart Hospital**, Hobart [18]: S Walker (Surgeon), D Stary, A Beasley (Interventionists), D Dunbabin (Stroke Physician)

**Royal Melbourne Hospital**, Melbourne [57]: S Davies (Neurologist), N Atkinson, B Allard, W Cambell, P Field, P Milne (Surgeons), B Tress, P Mitchell, B Yan (Interventionists)

**Princess Alexandra Hospital**, Brisbane [48]: T McGahan, A Wong (Neurologists), J Quinn M Ray, S Gett, P Woodruff (Surgeons), D Leggett (Interventionist)

### *Belgium*

**University Hospital Antwerp**, Antwerp [10]: J Hendriks, P Cras (Neurologists), O d'Archambeau (Interventionist), P Van Schil (Surgeon)

**Imelda Ziekenhuis**, Bonheiden [3]: L DeJaegher (Neurologist), P Peeters, J Verbist (Surgeons and Interventionists)

**AZ Sint-Jan Brugge-Oostende, Campus Brugge, Brugges [18]:** G Vanhooren (Neurologist), Jan De Letter (surgeon & Interventionist)

**Cliniques Universitaires St Luc, Bruxelles [1]:** A Peters (Neurologist), V Lacroix, P Astarci (Surgeons), F Hammer, R Verhels

**AZ St Blasius, Dendermonde [5]:** M Bosiers (Surgeon and Interventionist), E van Buggenhout (Neurologist), K Deloose (Surgeon and Interventionist)

*Canada*

**Foothills Medical Centre, Calgary [4]:** M Hill (Neurologist), W Morrish, M Hudion, W Hu (Interventionists), G Sutherland, J Wong (Surgeons)

**CHUM Notre-Dame Hospital, Montreal [30]:** D Roy (Interventionist), S Lanthier, S Lanthier, N, Daneault, L-H Lebrun (Neurologist), A Weill, F Guilbert, J raymond, G Soulez, V Oliva, M-F Giroux, J-F Blair, JL Caron (Surgeons)

*Finland*

**Helsinki University Central Hospital, Helsinki [33]:** M Kaste (Neurologist), M Skalej (Interventionist), Z Halloul (Surgeon)

*Germany*

**Otto von Guericke University, Magdeburg [9]:** M Görtler (Neurologist), M Skalej (Interventionist), Z Halloul (Surgeon)

*Ireland*

**Beaumont Hospital, Dublin [4]:** J Moroney (Neurologist), J Thornton, P Brennan (Interventionists), A Leahy, C Kelly (Surgeons)

*New Zealand*

**Auckland City Hospital, Auckland [40],** J Stewart (Interventionist), PA Barber (Neurologist), A Holden (Interventionist), A Hill, R Bouchier (Surgeon)

*Norway*

**Rijkshospitalet University Hospital, Oslo [16]:** SJ Bakke (Interventionist), M Skjelland (Neurologist), K Krohg-Sørensen (surgeon), B Tennøe (Interventionist)

*Poland*

Institute of Psychiatry and Neurology (2nd Department of Neurology & Department of Neuroradiology) & Medical University of Warsaw (2nd Department of General,

Vascular and Oncological Surgery), Warsaw [20]: A Czlonkowska, J Jedrzewska (Neurologists), J Polanski, P Bialek, Z Biejat (Surgeons), A Kobayashi, W Czepiel, M Lelek, A Dowzenko (Interventionists)

*Slovenia*

**University Medical Centre**, Ljubljana [12]: B Zvan (Neurologist), Z Milosevic (Interventionist), J Kirbis (Surgeon)

*Spain*

**Hospital Clinic**, Barcelona [18]: A Chamorro (Neurologist), J Blasco, L San Roman, J Macho (Interventionists), V Rimbau (Surgeon), V Obach (Neurologist)

**Parc Taulí Sabadell Hospital**, Barcelona [33]: D Canovas (Neurologist), Jordi Estela (Neurologist), J Perendreu, J Branera (Interventionist), A Gimenez Gaibar (Surgeon)

*Sweden*

**Malmö University Hospital**, Malmö [67]: A Gottsater (Neurologist), K Ivancev (Interventionist) T Maetzsch (Surgeon), B Sonesson, K Björres (Surgeons and Interventionists)

**Sodersjukhuset**, Stockholm [55]: P Konrad (Surgeon), T-B Kall (Neurologist), J Formgren, M Delle, N Nyman (Interventionists), P Gillgren, R Takolander, B Berg (Surgeons)

**The Karolinska Institute**, Stockholm [5]: N Wahlgren (Neurologist), T Andersson, M Soderman (Interventionists), J Malmstedt, C Wahlgren (Surgeons)

*Switzerland*

**University Hospital Basel**, Basel [94]: P Lyrer, ST Engelter, LH Bonati, F Fluri, (Neurologists), E-W Radue, AL Jacob, S Wetzel (interventionists), P Stierli, M Wasner (Surgeons)

**University Hospital of Geneva**, Geneva [16]: R Sztajzel (Neurologist), A Kalangos, N Murith (Surgeons), K Lovblad, D Ruefenacht (Interventionists), Christophe Bonvin

**Centre Hospitalier Universitaire Vaudois**, Lausanne [12]: P Michel, S Binaghi (Interventionist), P Ruchat (Surgeon), L Hirt (Neurologist)

*The Netherlands*

**Academic Medical Centre**, Amsterdam, Amsterdam [56]: PJ Nederkoorn, YB Roos (Neurologists), J Reekers (Interventionist), M Koelemaij (Surgeon)

**UMC St Radboud**, Nijmegen [13]: LJ Schultze Kool, FE De Leeuw (Neurologists), JD Blankensteijn, JA van der Vliet (Surgeons)

**Erasmus Medical Centre**, Rotterdam [75]: PJ Koudstaal (Neurologist), JM Hendriks, MRHM van Sambeek, HJM Verhagen, H van Urk (Surgeons), PMT Pattynama, LC van Dijk (Interventionists)

**Isala Klinieken**, Zwolle [14]: P Van den Berg (Neurologist), B van Hasselt (Interventionist), F de Beer, D Zeilstra (Surgeons)

**The Haga Teaching Hospitals**, The Hague [45]: A Mosch, R Keunen, SF de Bruijn (Neurologists), CMA Bruijninx, B Knippenberg, J Wever (Surgeons), H van Overhagen, F Treurniet, L van Dijk (interventionists)

**Medical Centre Haaglanden**, The Hague [3]: J Boiten (Neurologist), G Lyklama a Nyeholt, B van der Kallen (Interventionists), A de Vries, A de Mol van Otterloo (Surgeons)

**University Medical Centre**, Utrecht [270]: LJ Kapelle (Neurologist), GAP de Kort, TH Lo, WPThM Mali (Interventionists), F Moll, H Verhagen, GJ de Borst (Surgeons), HB van der Worp (Neurologist)

*United Kingdom*

**Birmingham Heartlands Hospital**, Birmingham [11]: RA Shinton (Neurologist), P Crowe (Interventionist), A Bradbury, M Gannon, L Papp, JM Scriven, T Wilmink (Surgeons), Scriven (Neurologist)

**North Bristol NHS Trust, Frenchay Hospital**, Bristol [13]: N Baldwin (Stroke Physician), L Jones, M Thornton (Interventionists), T Baker, D Mitchell, E Munro (Surgeons)

**Addenbrookes Hospital**, Cambridge [5]: P Martin (Neurologist), N Higgins (Interventionist), PJ Kirkpatrick, K Varty (Surgeons)

**Western Infirmary**, Glasgow [5]: J Moos (Interventionist), KR Lees (Neurologist), RD Edwards (Interventionist), AJ MacKay, P Rogers (Surgeons)

**Liverpool Royal Infirmary [21] and The Walton Centre**, Liverpool [7]: G Gilling-Smith (Surgeon), DA Gould, RG McWilliams, H-C Nasser, PL Harris, JA Brennan (Surgeons), JP Enevoldsen, R White (Neurologists)

**University College Hospital**, London [51]: MM Brown (Neurologist), R Jaeger, S Brew, J Brookes (Interventionists), C Bishop, N Kitchen (Surgeons)



**Royal Free Hospital**, London [1]: G Hamilton (Surgeon), D McCabe (Neurologist), A Platts, J Tibballs, N Davis (Interventionists), D Baker (Surgeon)

**St. Mary's Hospital, Imperial College Healthcare NHS Trust**, London [13]: J Chataway (Neurologist), M Hammady (Interventionist), I Malik (Cardiologist/Interventionist), Nick Cheshire, J Wolfe, M Jenkins, R Gibbs (Surgeons)

**St George's University of London and St George's NHS Healthcare Trust**, London [58]: H Markus, A Pereira (Neurologists), G Cloud (Stroke Physician), A Belli, A Clifton, R Morgan (Interventionists), A Halliday, A Thompson, R McFarland (Surgeons)

**Manchester Royal Infirmary**, Manchester [2]: G Subramanian (Stroke Physician), KG Prakash (Neurologist), F Serracino-Inglott (Surgeon and Interventionist), JV Symth, MG Walker (Surgeons)

**University Hospital of South Manchester, Wythenshawe**, Manchester [58]: C McCollum (Neurologist), P O'Neill (Stroke Physician), GE Gamble (Neurologist), R Ashleigh, S Butterfield (Interventionists), A Nasim, J Wong (Surgeons)

**Newcastle Acute Hospitals NHS Foundation Trust**, Newcastle-Upon-Tyne [108]: P Dorman, SA Dixit, S Louw, M Davis, H Rodgers. (Neurologists) G Ford, A Dyker (Stroke Physicians), A Golkar, S Macdonald, J Rose, V Jayakrishnan, R Jackson (Interventionists), D Mendelow, G Stansby, M Wyatt, D Lambert, T Lees, M Clarke (Surgeons)

**Lancashire Teaching Hospitals NHS Trust**, Preston [2]: DM Seriki (Interventionist), R Guta, S Puneekar (Neurologists), S D'Souza (Interventionist), A Egun, G Thomson (Surgeons)

**Sheffield Teaching Hospitals NHS Foundation Trust**, Sheffield [151]: G Venerables (Neurologist), J Beard, D Dodd, R Lonsdale, R Nair, A Nassef, S Nawaz (Surgeons), P Gaines, T Cleveland (Interventionists)

## Appendix 6 – The International Carotid Stenting Study Protocol<sup>2</sup>

### Protocol Summary

**Background:** Clinical trials have shown that carotid surgery prevents stroke but also has significant morbidity. Stenting has become an established alternative treatment for coronary and peripheral vascular disease and has the advantage of avoiding general anaesthesia and neck incision. In July 1997, randomisation was completed in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS). The results did not show a difference in the major risks or benefits of carotid angioplasty and surgery, but the trial did show that both methods still carry a significant risk of causing a stroke. Techniques of carotid angioplasty have improved and stenting is increasingly used. The International Carotid Stenting Study (ICSS or CAVATAS 2) is a follow-on study to CAVATAS designed as an international, multicentre, randomised trial, which will evaluate stenting of carotid artery stenosis in patients with cerebrovascular disease.

**Centre requirements:** A neurologist or physician with an interest in stroke; a surgeon with expertise in carotid endarterectomy and an interventionalist with expertise in carotid angiography and the techniques of angioplasty and stenting.

**Inclusion criteria:** Symptomatic atheromatous carotid stenosis, > 50% by NASCET criteria, suitable for stenting and surgical endarterectomy.

**Treatments:** Patients will be randomised in equal proportions to be treated by carotid endarterectomy or stenting. New design of stents, filters and protection devices will be incorporated into the study to allow tracking of new technology if approved by the Steering Committee. Surgery can be performed with local or general anaesthesia.

**Sample size:** N = 1500 patients from fully enrolled centres. Sample size calculations show that the 95% confidence intervals will be  $\pm 3.0$  percentage points for the outcome measure of 30 day stroke, myocardial infarction and death rate and  $\pm 3.3$  percentage points for the outcome measure of death or disabling stroke during follow-up.

**Primary outcome measure:** Long term survival free of disabling stroke.

**Secondary outcome measures:** Any stroke, myocardial infarction or death within 30 days of treatment, treatment-related cranial nerve palsy or haematoma. Stenosis (>70%) and occlusion on ultrasound follow-up. Transient ischaemic attack. Stroke during follow-up. Further treatment procedure. Quality of life and economic measures.

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<sup>2</sup> The ICSS protocol v3.2 is reproduced in an abridged version in this thesis.

## Background

Stroke is the major cause of acquired adult physical disability and is responsible for 12% of all deaths in the UK. Reducing the burden of stroke is one of the priorities of the recent government white paper, *Saving Lives: Our Healthier Nation*. In Europe alone, there are approximately one million new cases of stroke a year. Atherosclerotic stenosis of the carotid artery is an important cause of stroke, which may be heralded by a transient ischaemic attack (TIA) or minor stroke, which recovers without serious disability. The risk of recurrent stroke in recently symptomatic patients with severe carotid stenosis is as high as 28% over two years. The European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) have demonstrated convincingly that this risk is reduced significantly by carotid endarterectomy.<sup>1,2</sup> Carotid surgery has therefore become a standard treatment for these patients. However, the trials showed a significant risk of stroke or death resulting from surgery of between 6 and 8%. Surgery also caused significant morbidity from myocardial infarction during the general anaesthetic used in most centres and minor morbidity, including cranial nerve palsy and wound haematoma from the incision. An increasing number of surgeons are performing carotid endarterectomy under local anaesthesia in the belief that it reduces the risks, although there is currently little evidence to support this practice, until the data from the General Anaesthesia versus Local Anaesthesia for Carotid Endarterectomy (GALA) trial are reported.

Stenting is a new method of treating carotid stenosis, which has evolved from the technique of percutaneous transluminal angioplasty (PTA). Stenting avoids some of the hazards of surgery and has become an established treatment for peripheral and coronary artery stenosis. Stenting is less invasive than carotid endarterectomy and has advantages in terms of patient comfort, because the procedure avoids an incision in the neck, and is usually conducted under local anaesthesia. Hospital stay need only be for 24 hours after treatment if uncomplicated. When given the choice, stenting is preferred by many patients. On the other hand, stenting does not remove atheromatous plaque, has not been shown to prevent stroke and may have an unacceptable incidence of restenosis. We therefore propose a multicentre randomised trial to compare carotid stenting with carotid surgery.

## Previous work in the field

*Percutaneous transluminal angioplasty:* A number of groups have published series of patients with carotid stenosis treated by PTA. The cumulative total of patients in these series is over 1000, with a reported major complication rate of less than 5% at the time of the procedure.<sup>3</sup> These data suggested that carotid PTA has a similar risk to carotid

surgery, but the results could not be taken as definitive because none of the data were from randomised trials. We therefore started a randomised trial, known as the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) in 1992. We completed randomisation in July 1997.

*Results of CAVATAS:* 560 patients were entered, from 24 centres in the UK, Australia, Canada, Finland, Germany, Italy, Spain, Switzerland, and the USA. Patients with carotid stenosis suitable for surgery were randomised between PTA (n=251) and carotid surgery (n=253). Patients with carotid stenosis unsuitable for surgery (n=40) and patients with vertebral artery stenosis (n=16) were separately randomised between PTA and medical care alone. The number of patients in these last 2 groups was too small to form any firm conclusions. The analysis has therefore been restricted to the 504 patients with carotid stenosis randomised between PTA and surgery.<sup>4</sup> Baseline variables were well matched. Almost all patients had severe stenosis (mean 86%). The 30-day outcome events were almost identical in the two groups with a rate of death or any stroke lasting more than 7 days of 10.0% after angioplasty and 9.9% after surgery, giving a hazard ratio of 1.01 (95% CI:0.56,1.81) (NS). Analysis of the other risks of treatment has confirmed that PTA was safer than surgery in terms of minor morbidity. Cranial or peripheral nerve palsy was reported in 9% of surgical patients, but not in any PTA patients (p<0.0001). Haematoma requiring operation or prolonging hospital stay was reported in 7% of surgical patients compared with 1% of PTA patients (p<0.0015). PTA also appeared safer than surgery with regard to perioperative myocardial infarction, which occurred in 0.8% of surgical patients, but not in any PTA patients. Survival analysis from randomisation showed no difference in outcome events of ipsilateral stroke and any disabling stroke or death during follow up for up to 3 years with very few events in either arm after the treatment period, suggesting that both treatments were equally effective at preventing stroke. However, 19% of PTA patients had stenosis of >70% or occlusion by ultrasound criteria at 12 months after randomisation compared to 5% of surgical patients (p<0.0001). Restenosis was not associated with new symptoms, but long-term follow up is limited

*Causes and timing of stroke in CAVATAS:* The cause of stroke within 30 days of first treatment in CAVATAS was cerebral infarction in 22 patients in the PTA group and 20 patients in the surgery group. Primary cerebral haemorrhage caused the other three strokes in the PTA group and 2 strokes in the surgery group. All but one stroke was ipsilateral to the randomised artery. Surprisingly, a significant proportion of these treatments related strokes were delayed after the day of treatment. Eight (36%) of the strokes in PTA patients occurred between the second and 21<sup>st</sup> day after treatment. Delayed stroke was also found in 6 (27%) of the surgical group between the third and 10<sup>th</sup>

day after operation. Delayed stroke may account for the relatively high rate of 30-day morbidity in CAVATAS at 10% compared to 7.5% in ECST and 5.8% in NASCET.

*Carotid stenting:* Stents suitable for carotid use have only become available recently. The CAVATAS Steering Committee decided to allow the use of stents at the discretion of the interventionist. Stents were used in 55 patients randomised to PTA, usually as a secondary procedure i.e. after initial balloon dilation. The indication for using a stent in these cases was usually an inadequate angiographic result and in some cases stents were deployed because of stroke at the time of full balloon inflation, as a 'bail-out' procedure. Only one stroke occurred at the time of stent deployment (1.8%), although there were a small number of delayed strokes after stenting.

*The need for a trial of carotid stenting:* It would be inappropriate to use the results of CAVATAS to propose the widespread introduction of PTA for the treatment of carotid stenosis as an alternative to surgery, because the 95% confidence interval surrounding the 10% risk of any stroke within 30 days of treatment in the surgical and angioplasty groups is  $\pm 5\%$ . Nevertheless, the results support the need for further randomised studies. The interventional technique used to treat carotid stenosis has evolved over the 7 years since we started CAVATAS, from the use of simple inflatable balloon catheters at the beginning of the trial to the increasing use of stenting towards the end of the trial. Initially stents were used only as a secondary procedure after full balloon inflation for inadequate results or complications of treatment. The desire to prevent these complications and superior early results in stented patients has led to the increasing use of the technique of primary stenting in which the intention is to deploy a stent in every patient before dilation (but after pre-dilatation to allow the atraumatic passage of the stent) of the artery<sup>5</sup>. Primary stenting is now accepted as best practice<sup>5</sup> and has become the radiological technique of choice for carotid stenosis, replacing balloon angioplasty.

*Advantages of carotid stenting:* The majority of major strokes after carotid PTA are the result of dissection of the carotid artery at the time of balloon inflation with subsequent thrombosis. It is believed that stenting is safer than simple balloon angioplasty because embolisation, dissection and closure of the carotid artery are less likely to occur.<sup>6,7</sup> The subgroup analysis of stented patients in CAVATAS is consistent with this suggestion. The adverse consequences of dissection are minimised, because the stent maintains laminar flow across the stenosis and seals the site of dissection, preventing a free intimal flap. In addition, the stent mesh limits the size of any thrombus or atheromatous debris that may be dislodged from the plaque at the time of dilation of the artery. Superior dilation achieved by stenting compared with balloon angioplasty may also reduce the rate of stroke in the early post-treatment period. In the coronary circulation, stenting has

been shown to produce superior outcomes compared with balloon angioplasty.<sup>8,9</sup> Individual case series suggest that carotid stenting has a similar rate of procedural stroke to that of carotid surgery,<sup>6,7</sup> while a recent registry reported a total of 2,048 patients from 24 centres undergoing carotid stenting with a complication rate of stroke and death within 30 days of treatment of 5.8%.<sup>10</sup>

*Disadvantages of carotid stenting:* Although acceptable safety at the time of stenting has been suggested by the case series and registry data, stenting has not been subjected to a randomised trial in comparison to conventional surgical treatment and has not been demonstrated to prevent stroke, which is the aim of treatment. Stenting does not remove atheromatous plaque and stents may stimulate neo-intimal hyperplasia. In the long term it is likely that the rate of restenosis will be greater after stenting than after carotid surgery, which could well result in an unacceptable rate of long-term stroke recurrence. There is an important need to establish the efficacy of carotid stenting in comparison to surgery before the technique is widely introduced without adequate trial based evidence.

*Antiplatelet therapy:* In cardiological practice, ischaemic complications during coronary stenting have been shown to be significantly reduced by using a combination of two antiplatelet agents, ticlopidine and aspirin. In one coronary trial, stent thrombosis was reduced from 3.6% in patients assigned aspirin alone down to 0.5% in patients assigned aspirin and ticlopidine.<sup>11</sup> A recently completed trial has shown that similar results with less risk of side effects can be achieved during coronary stenting by using the combination of clopidogrel with aspirin.<sup>12</sup> It is likely that this combination would also reduce the risks of stroke during carotid stenting. A pilot study is currently being carried out at one of the centres to establish the safety of the combination of clopidogrel and aspirin given before and for 30 days after carotid stenting. It is likely that this will become standard therapy. Most surgeons currently believe that combination antiplatelet therapy during surgery is hazardous because of excess bleeding.

*Economic and quality of life considerations:* Quality of life and general health status were assessed in CAVATAS using the SF36 and EuroQol EQ-5D questionnaires. These showed a similar quality of life for patients randomised to either treatment. Operating and radiology suite costs were similar in a sample of patients at two UK centres, but surgery was associated with a longer hospital stay and greater use of ITU beds. Surgery was therefore considerably more expensive than angioplasty (mean difference £946).<sup>13</sup> However, the mean cost of an angioplasty increased from £1086 to £1864 if a stent was used. The use of stents in every case is therefore likely to increase the costs of stenting close to that of surgery, but this might be counterbalanced by performing carotid stenting as a day case procedure. Surgical length of stay is also declining. Follow up costs might

be very different if restenosis is more frequent in one arm. Economic analysis will therefore be an important component of ICSS.

### **Aims of ICSS**

To compare the risks, benefits and cost effectiveness of a treatment policy of referral for carotid stenting compared with referral for carotid surgery.

### **Trial design**

ICSS is an international, multicentre, randomised, controlled, open, prospective clinical trial comparing carotid surgery with carotid stenting.

### **Participating centre requirements**

Each centre must have a neurologist or physician with an interest in stroke who will see patients prior to randomisation and for follow up. Carotid endarterectomy must be carried out by designated surgeons with expertise in the operation. Carotid stenting will be carried out by designated consultant interventionists with expertise in carotid angiography and the techniques of angioplasty and stenting. Good collaboration between the neurologists, surgeons and interventionists is essential and centres should have regular neurovascular meetings. Attendance at training sessions in carotid stenting provided by credentialing centres will be required for all interventionists prior to participation. Participating centres will be required to submit *curriculum vitae* for all participating clinicians and an audit of recent carotid surgery and PTA/stenting results. An accreditation committee will decide if they have appropriate experience and expertise to join the study. As a guide, surgeons and interventionists will be expected to show a stroke and death rate within 30 days of treatment, consistent with the centres in ECST who had an average rate of 7.0% with a 95% confidence interval of 5.8 to 8.3%.<sup>1</sup> Surgeons will be expected to have performed a minimum of 50 carotid operations with a minimum annual rate of at least 10 cases per year. Interventionists will similarly be expected to have performed a minimum of 50 stenting procedures, of which at least 10 should be in the carotid territory. Centres where there is little or no experience of carotid stenting may join ICSS for a probationary period in order to gain the minimum experience of ten carotid stenting procedures required to join the trial fully. The results in patients randomised during the probationary period will be analysed separately.

All centres will have to provide proof of Ethical Committee Approval for the study before commencing randomisation.

## **Probationary centres**

Probationary centres will be required to fulfil all the other requirements for entry, but will not have to provide audited data on ten carotid stenting procedures initially.

Probationary centres will randomise patients within the ICSS protocol between surgery and stenting. Individual interventionists who are not able to satisfy the credentialing requirements will be identified as probationary investigators. Stenting procedures carried out during the probationary period must be proctored by an experienced carotid interventionist, until the proctor is satisfied that the interventionist(s) at the centre can satisfactorily carry out procedures unproctored. Probationary interventionists will become fully enrolled in ICSS when both the proctor is satisfied that the interventionist can perform procedures unsupervised and the interventionist has 10 or more successfully completed cases in the trial, with an acceptable complication rate. When an investigator has done sufficient successful procedures, the trial office will get comments from the relevant proctor, and then have any decision to promote the investigator or centre signed off by the chair of steering committee.

## **Proctoring**

Proctors for probationary centres will be approved by the accreditation committee in consultation with the probationary centre via the central ICSS office. Probationary centres may suggest an appropriate proctor, but he or she will require prior approval from the accreditation committee, based on review of the proctor's experience of carotid stenting. It is the responsibility of the probationary interventionist to make contact with an approved ICSS proctor and to ensure a convenient date is organised for the stenting procedure at which the proctor can be present. Copies of the relevant radiology should be available for the proctor for review prior to starting the stenting procedure. This should be done prior to randomisation if there was any doubt about the suitability of the patient for stenting. In the event of a centre requiring proctoring for surgery the same procedure will apply.

It is the responsibility of the probationary interventionist and the proctor in discussion to ensure the lesion is appropriate for treatment (e.g. sufficiently severe), that the patient has received appropriate premedication (e.g. a combination of clopidogrel and aspirin) and that the lesion is suitable for stenting. They should agree the type, range and sizes of equipment required and the probationary interventionist should ensure that this equipment is available to complete the procedure. If any of these conditions are not met, the procedure should be abandoned and if appropriate rescheduled for another occasion.

Catheter or arch angiography is not required in ICSS prior to randomisation if the centre does not routinely perform angiography prior to treatment. However, the centre



interventionist, the proctor and the patient should be aware that if preliminary angiography at the time of planned stenting shows a lesion which is not suitable for stenting, the procedure should be abandoned and the patient referred for surgery, or continued medical management. This type of cross over is envisaged in the trial design.

Where a centre has an adequately qualified surgeon and interventionist they may supervise surgeons and interventionists at the same centre whose experience would not initially qualify them for the trial until they have gained sufficient experience. These new investigators must enrol with the central ICSS office (see participating centre requirements).

### **Inclusion criteria**

- Symptomatic, extracranial, internal or bifurcation, atheromatous carotid artery stenosis that is suitable for both stenting and surgery and is deemed by the randomising clinician to require treatment.
- The severity of the stenosis of the randomised artery should be at least 50% (as measured by NASCET method or non-invasive equivalent).
- Symptoms must have occurred in the 12 months before randomisation. It is recommended that the time between symptoms and randomisation should be less than 6 months, but patients with symptoms occurring between 6 and 12 months may be included if the randomising physician considers treatment indicated.
- The patient must be clinically stable following their most recent symptoms attributable to the stenotic vessel.
- Patients must be willing to have either treatment, be able to provide informed consent, and be willing to participate in follow up.
- Patients must be able to undergo their allocated treatment as soon as possible after randomisation.
- Any age greater than 40 may be included. There is no upper age limit.
- Patients should only be randomised if the investigator is uncertain which of the two treatments is best for that patient at that time.

### **Exclusion criteria**

- Patients refusing either treatment.

- Patients unable or unwilling to give informed consent.
- Patients unwilling or unable to participate in follow up for whatever reason.
- Patients who have had a major stroke with no useful recovery of function within the territory of the treatable artery.
- Patients with a stenosis that is known to be unsuitable for stenting prior to randomisation because of one or more of:
  - Tortuous anatomy proximal or distal to the stenosis
  - Presence of visible thrombus
  - Proximal common carotid artery stenotic disease
  - Pseudoocclusion ('string sign').
- Patients not suitable for surgery due to anatomical factors e.g. high stenosis, rigid neck.
- Patients in whom it is planned to carry out coronary artery bypass grafting or other major surgery within 1 month of carotid stenting or endarterectomy.
- Carotid stenosis caused by non-atherosclerotic disease e.g. dissection, fibromuscular disease or neck radiotherapy.
- Previous carotid endarterectomy or stenting in the randomised artery.
- Patients in who common carotid artery surgery is planned.
- Patients medically not fit for surgery.
- Patients who have a life expectancy of less than two years due to a pre-existing condition, e.g. cancer.

### Non-randomised patients

An anonymised log will be kept of patients undergoing treatment for carotid stenosis by the trial investigators but not randomised at the participating centres. Patients undergoing stenting but not randomised should also be included on a suitable registry, such as EUROCAST.

## **Consent**

Written witnessed, informed consent will be obtained from all patients and a copy must be retained by the randomising centre. All patients will be provided with a written explanation of the study.

## **Randomisation**

Randomisation will be by a telephone call or fax to a computerised service provided by the Oxford Clinical Trials Service Unit. Randomisation will be stratified by centre with minimisation of the main risk factors and balanced between the arms. Patients who need treatment of both carotid arteries will only be randomised for the carotid artery to be treated first. Patients can only be randomised once.

## **Investigations before randomisation**

The following investigations are required: Routine haematology (FBC, platelets), blood biochemistry (renal function, blood sugar, cholesterol), chest x-ray, ECG, brain CT or MRI scans. The brain scan is required to exclude other pathology, to identify existing infarcts and to provide a baseline reference against which any subsequent infarction or haemorrhage can be assessed. Copies of the CT or MRI scans should be sent to the ICSS office.

## **Carotid imaging**

Mandatory investigation is required for entry into the study to confirm the presence and severity of the ipsilateral stenosis and to assess contralateral carotid disease. The following are acceptable:

1. Arch arteriogram showing both carotid bifurcations,
2. Selective catheter carotid angiography showing the randomised carotid artery with non-invasive investigation of the contralateral carotid bifurcation.
3. Bilateral magnetic resonance carotid angiograms together with a concordant ultrasound scan.
4. Bilateral spiral CT angiograms together with a concordant ultrasound scan.
5. Bilateral duplex and Doppler ultrasound scan, only if this is standard practice to treat on the basis of ultrasound alone in individual centres and the centre has been able to provide proof of the reliability of their ultrasonographic imaging through clinical audit.

The following data from the pre-randomisation imaging will be sent to the Central Office for review:

1. A copy of the written reports of the studies.

2. A film copy of the view of the vessel to be treated showing the stenosis at its most severe.
3. A film copy of the view of the contralateral vessel showing any stenosis at its most severe.
4. Velocity data from the ultrasound examination.

Patients who are randomised to stenting after ultrasound or other non-invasive investigation, in which subsequent angiography, prior to stenting, reveals one or more exclusion criteria should be treated by surgery, if appropriate, or medical care only if surgery is not appropriate (e.g. because the stenosis is less than 50%). These patients will continue follow up in the trial and will be analysed on an intention to treat basis. A similar approach should be taken to patients randomised to surgery in whom contraindications to surgery emerge after randomisation.

### **Ultrasound**

Ultrasound study of the carotid artery to be treated will be performed at or before randomisation, at one month after treatment and then annually after randomisation in all patients. The following information is required for each study: Peak systolic velocity of internal carotid artery (PSV ICA), end diastolic velocity of internal carotid artery (EDV ICA), peak systolic velocity of common carotid artery (PSV CCA). The accuracy of individual ultrasound laboratories will be audited by comparing the pretreatment ultrasound examination against catheter angiography films, which will be available in patients randomised after angiography and in all the patients treated by stenting.

### **Baseline data**

Baseline data collected at randomisation will include demographic data; existing medical risk factors; neurological symptoms including an assessment of disability using the Modified Rankin Scale; current antiplatelet therapy and blood pressure. Films and/or reports of pre-randomisation imaging as detailed above and in all cases the results of Doppler ultrasound as detailed below are required to allow assessment of any subsequent stenosis.

### **Baseline assessment**

Patients will be seen by the study neurologist or physician interested in stroke prior to randomisation to confirm suitability for the study.

### **Stenting protocol**

Stenting will be carried out as soon as possible after randomisation using percutaneous transluminal interventional techniques from the femoral, brachial or common carotid

artery by a designated interventional consultant using an appropriate stent. A cerebral protection system should be used whenever the operator thinks one can be safely deployed. Stents and other devices used in the trial must be CE marked and approved by the Steering Committee. Pre-medication will be discretionary. The combination of aspirin and clopidogrel is recommended as the antiplatelet regime of choice to cover the period of stenting and for a minimum of 4 weeks afterwards. Intra procedural heparin is mandatory at a dose determined by the operator, post procedural heparin may be given according to clinical requirements. Patients should be monitored for changes in their neurological status and heart rate throughout the procedure. If femoral or brachial access is being used a long sheath introducer or a guiding catheter is placed in the common carotid artery allowing pre-dilation and stent placement under direct arteriographic imaging. Atropine, or a similar agent, must be administered prior to stent deployment to counteract any effects on the carotid artery baroreceptors, which could lead to severe bradycardia and / or asystole. Virtually all patients will require pre-dilatation of the stenosis by balloon angioplasty prior to stent deployment. This will minimise the embolic load caused by passage of the endoluminal stent through the stenosis. The size of the pre-dilatation balloon will be determined by the size of the delivery system being used. Further balloon dilation of the stent will usually be required to ensure apposition of the stent against the arterial wall. Angiographic images showing the stenosis at its most severe prior to stenting and the same view and any other view that demonstrates the maximum residual stenosis after stenting must be sent to the Central Office. Details of the procedure, including all peri-procedural complications, drug therapy and devices used in the procedure, must be reported and the stenting and cerebral protection technical data sheet returned to the trial Central Office.

### **Endarterectomy protocol**

Endarterectomy is to be done as soon as possible after randomisation by a designated consultant surgeon who has been approved by the Credentials Committee. It is to be carried out using whichever procedures are standard at the individual centre, including the use of local or general anaesthesia, shunts or patches as required by the operating surgeon. Standard or eversion endarterectomy may be performed.

### **Reporting of suspected problems with surgical or stenting techniques at individual centres**

If the local investigator, or other member of the team, at a trial centre has concern about the outcome of their trial procedures, they should inform the ICSS trial office, which will organise a blinded assessment of the relevant outcome events. This will be submitted by the central office to the chairman of the data monitoring committee who may recommend

further action, such as suspending randomisation at the centre. Similarly, the database manager at the trial office will monitor outcome events and if there are two consecutive deaths or three consecutive major events at a single centre within 30 days of treatment in the same arm of the study, then assessment of the events will be triggered. A cumulative major event or death rate of more than 10% over 20 cases would also trigger careful assessment of the relevant outcome events.

### **Medical treatment**

All patients will receive best medical care including antiplatelet therapy or anticoagulation (when appropriate) and control of medical risk factors such as hypertension, smoking and hyperlipidaemia before treatment and throughout the period of follow up.

### **Prevention of thrombosis**

Therapy to prevent thrombosis during or soon after surgery or stenting will be prescribed according to standard practice in each centre. This may include heparin, dextran, aspirin, dipyridamole, ticlopidine, clopidogrel, or a combination of aspirin and another antiplatelet agent. Glycoprotein IIb/IIIa antiplatelet receptor antagonists will not be used routinely.

### **Follow up**

Patients will be followed up by a neurologist or a physician interested in stroke at the participating centres at 30 days after treatment, 6 months after randomisation and then annually after randomisation. All post-procedural complications occurring within thirty days after the procedure will be reported to the central office at the 30 day follow up. At each visit, levels of stroke related disability will be assessed using the modified Rankin Scale and any relevant outcome events will be notified to the Central Office. A Doppler ultrasound will be used to measure carotid arterial diameter to assess patency at one month after treatment and then annually after randomisation. In addition, ultrasound re-examination and CT or MRI scan should be performed in-patients who have any transient ischaemic events and / or stroke during follow up. The duration of follow up will be a minimum of 5 years (or until termination of the trial if earlier). At the 5 year follow up, patients will be asked if they are willing to continue follow up, in which case annual follow up will continue up to a maximum of 10 years from randomisation.

### **Sample size calculations and recruitment**

The planned sample size is 1500. We do not anticipate any large difference in the principal outcome between surgery and stenting. We propose to estimate this difference and present a confidence interval for difference in 30-day death, stroke or myocardial

infarction and for three-year survival free of disabling stroke or death. For 1500 patients, the 95% confidence interval will be the observed difference  $\pm$  3.0 percentage points for the outcome measure of 30 day stroke, myocardial infarction and death rate and  $\pm$  3.3 percentage points for the outcome measure of death or disabling stroke over three years follow up. However, the trial will have the power to detect major differences in the risks of the two procedures, for example if stenting proves to be much riskier than surgery or associated with more symptomatic restenosis. The difference detectable with power 80% are 4.7 for 30 day outcome and 5.1 percentage points for survival free of disabling stroke. Similar differences are detectable for secondary outcomes. We expect to achieve this recruitment within 6 years.

## Principal research questions to be addressed

### Primary analysis

- What is the difference in the long-term rate of fatal or disabling stroke in any territory of patients with severe symptomatic stenosis after randomisation to a policy of carotid stenting compared to surgery?

### Secondary analysis

- What are the differences in mortality and morbidity within 30 days of carotid stenting compared to surgery?
- What is the rate of symptomatic and asymptomatic restenosis after carotid stenting compared to surgery?
- What are the differences in the rate of ipsilateral stroke during follow-up after carotid stenting compared to surgery?
- What is the cost-effectiveness of carotid stenting compared to surgery?
- What are the risk factors for stroke within 30 days and during long term follow up (including those related to age, gender, symptoms, imaging, centre and technique)?

### Outcome events

- Any stroke or death.
- Transient ischaemic attack.
- Myocardial infarction within 30 days of treatment.
- Cranial nerve palsy within 30 days of treatment.

- Haematoma caused by treatment requiring surgery, transfusion or prolonging hospital stay.
- Stenosis greater than 70% or occlusion during follow up.
- Further treatment of the randomised artery by interventional radiology techniques or surgery after the initial attempt.
- Quality of life, health status and Health Service costs (see paragraph below).

### Outcome event reporting

Outcome events will be documented in detail by the investigating centre, censored after receipt at the central office to remove clues as to the treatment received, and then adjudicated by an independent neurologist. Patients suffering stroke should have a CT or MRI brain scan as soon as possible after the event. A film copy of this, together with a film copy of the pre-randomisation scan (if done) should be submitted together with a report of the event. The event report should include copies of discharge summaries; death certificates and post mortem results if relevant. Deaths of UK patients will be tracked by flagging patients against the UK Registry of Births and Deaths. Disability after stroke and cranial nerve palsy will be assessed 30 days and six months after treatment or onset, using the Modified Rankin scale. Duration of symptoms will be recorded and outcome events will be classified as disabling if the Rankin score is 3 or more at six months.

### Learning curve

Carotid stenting is a new procedure, while the techniques of carotid surgery are well established. It is likely that there will be a learning curve for carotid stenting and the results may improve with experience during the trial. However, we believe it is better that carotid stenting should be performed as part of a randomised clinical trial at this stage of its development, because this will ensure careful assessment and follow up of all patients treated in the trial and supervision from the Data Monitoring and Ethics Committee ensures that continuing treatment with the new technique remains ethical. The influence of the early part of the learning curve for carotid stenting will be limited by careful training of individual interventionists. The total experience of carotid PTA and stenting of individual interventionists will be recorded prior to entry into the trial. This will allow the average duration of the learning curve to be analysed, taking into account the current experience of the individual interventionists. This information may have implications for interpretation of the results of the trial and for the future training and supervision of the procedure. Similarly, there may be improvements in individual surgical or anaesthetic techniques during the trial.



### **Effect of changes in technology during the course of the study**

The field of carotid stenting is an area of fast changing technology. The protocol does not at present specify the type or manufacturer of the stents or protection devices to be used, but devices to be used in the trial will be CE marked and approved by the Steering Committee who will expect a peer reviewed report of device safety. More than one device may be recommended to allow the interventionist to tailor the choice of stent to the individual stenosis and to use new designs of stent or protection devices if appropriate. The protocol will not specify the technique to be used during carotid surgery. Decisions about the use of shunts or specific suture materials will be left to the individual surgeon. Local or general anaesthesia will be allowed in both arms. Technical details of surgical and stenting technique, including the manufacturer and type of stent used, the use of local or general anaesthesia, and the use of antithrombotic agents, will be recorded. The analysis will include a subgroup comparison of different techniques in both arms and the data will be presented to the DMC meetings to ensure that no one technique is significantly inferior to another. Randomisation will use a computer programme to minimise variation between centres and over time, so that equal numbers of patients will be entered into the stenting and surgery arms before and after any change in practice.

### **Health service research issues**

If the trial confirms the hypothesis that carotid stenting and surgery are equivalent in terms of the major risks of stroke and death, then the choice between the two procedures will be determined primarily by differences between the two procedures in other outcomes e.g. the disadvantage of a scar or cranial nerve palsy, or the effects of surgery on health related quality of life. If these differences are minor, the choice between the procedures will be made primarily on economic grounds. The effects of cranial nerve palsy may be detected by a minor increase in the disability score, but it is not easy to assess the effect of these outcomes during follow up on clinical examination alone. Quality of life and health status will therefore be assessed using the EuroQol (EQ5D) questionnaire<sup>14</sup> to compare patients' feeling of well-being, health and quality of life before and after stenting or surgery at one month, six months and annual follow up. The results will be analysed blind to treatment arm. The first questionnaire will be completed at the time of randomisation and subsequent questionnaires at each follow-up visit. The investigator performing randomisation or follow-up should ensure the patient completes the EQ5D at the same time. The English language version of the EQ5D has been modified to record the date on which it is completed and the patients trial number. Those centres using versions in other languages should also record the date and trial number on each completed form. If patients are too disabled to complete the questionnaires themselves,

the patient's carer may complete them. The EQ5D should be returned to the central office with the other trial forms.

Information on hospital resource use during the treatment and follow up, including the type and manufacturer of the devices employed in carotid stenting procedures, will be collected to measure treatment costs and estimate the costs of stroke and any consequences of restenosis (e.g. retreatment) during follow up. Unit costs will be obtained from a sample of representative centres. The costs of stroke caused by treatment are a major component of the total cost of treatment, and therefore have a major influence on cost effectiveness. As the additional length of stay in hospital resulting from stroke largely drives these costs, the prospective collection of length of stay data will be designed to capture the stroke-related data in addition to direct operative stay. The economic evaluation will address cost-effectiveness and cost-utility (cost per QALY). The latter will be estimated from patients' responses to the EuroQol (EQ-5D) questionnaires using the York MVH tariff. Uncertainty regarding specific parameters within the analysis will be subjected to a sensitivity analysis, and uncertainty around the point estimate of the cost utility ratio will be represented using cost-effectiveness acceptability curves. To inform the economic analyses, the preferences of potential patients and clinicians between carotid endarterectomy and carotid stenting given various differences in outcomes will be explored using the technique of conjoint analysis (discrete choice experiments). A sample of members of the general population (matched to the ICSS patients) and clinicians will be asked to complete a questionnaire after completion of randomisation, informed by the preliminary safety results. Preliminary work, structuring and piloting the conjoint analyses, will be undertaken earlier.

### **Stenosis after treatment**

Patency of the carotid artery will be monitored by Doppler ultrasound at a minimum of 30 days after treatment and then annually after randomisation. Restenosis should only be treated by further angioplasty or surgery if the patient has relevant new symptoms. Restenosis is usually the result of smooth muscle hypertrophy or neo-intimal hyperplasia, rather than recurrence of atherosclerosis and hence may not cause embolic stroke. Asymptomatic restenosis will not be an indication to retreat the lesion because the risk of disabling symptoms after restenosis is not known.

### **Crossovers**

Crossovers before any attempt to treat the randomised artery by the allocated treatment will be avoided unless clinically essential, because the trial data will be analysed by intention to treat. Patients who are randomised to stenting after ultrasound or other non-

invasive investigation, in whom subsequent angiography prior to stenting, reveals one or more exclusion criteria should be treated by surgery, if appropriate, or medical care only if surgery is not appropriate (e.g. because the stenosis is less than 50%). These patients will continue follow up in the trial and will be analysed on an intention to treat basis. A similar approach should be taken to patients randomised to surgery in whom contraindications to surgery emerge after randomisation. Patient refusal of the treatment to which they are randomised can be minimised by careful consent. Patients requiring re-treatment because of further symptoms should be re-treated with whichever treatment is most appropriate. This is also the case if the non-randomised carotid artery requires treatment. Patients in whom an attempt at stenting fails may proceed to early surgery if appropriate and vice versa.

### **Data analysis**

The data will be analysed by intention to treat using standard statistical tests by the trial statistician. The analyses will compare the treatment groups with respect to the length of time before treatment failure (i.e. occurrence of an outcome event) by means of the Mantel-Haenszel chi-squared test and Kaplan-Meier survival curves. Secondary analysis will compare the proportions of outcome events within 30 days of treatment. All analyses will be adjusted for centre and predetermined risk factors. Subgroup analyses will examine risk factors for outcome events and will examine the influence of different devices, surgical techniques and experience within the trial. Results at probationary centres will be analysed separately. The results of any interim data analysis will remain confidential to the trial statistician and Data Monitoring Committee until after completion or early discontinuation of the trial. Investigators and the Steering Committee will remain blind until such point.

### **Publication**

Publication of the results of ICSS will be prepared by the Central Office and circulated to participating centres for comment prior to submission of the manuscript for publication on behalf of all the ICSS collaborators.

### **Ethical Committee approval**

Multicentre Research Ethics Committee approval will be sought in the UK. In addition, individual centres are expected to obtain local ethical committee approval for the study.

### **Data Monitoring Committee**

The safety aspects of the trial will be overseen by a Data Monitoring Committee consisting of an independent neurologist, medical statistician surgeon and interventionist. The progress of the study will be assessed at regular intervals determined

by the Data Monitoring Committee. During the period of intake to the study, interim analyses of mortality and of any other information that is available on major endpoints (including serious adverse events believed to be due to treatment) will be supplied, in strict confidence, to the chairman of the Data Monitoring Committee, along with any other analyses that the Committee may request. In the light of these analyses, the Data Monitoring Committee will advise the chairman of the Steering Committee if, in their view, the randomised comparisons in ICSS have provided **both** (i) "proof beyond reasonable doubt" that for all, or for some, specific types of patients, one particular treatment is clearly indicated or clearly contraindicated in terms of a net difference in outcome, **and** (ii) evidence that might reasonably be expected to influence materially patient management. Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least 3 standard deviations in an interim analysis of a major endpoint may be needed to justify halting, or modifying, the study prematurely. This criterion has the practical advantage that the number of interim analyses is of little importance.

### Steering Committee

Steering Committee Committee, consisting of individuals participating in and independent of the trial with experience in stroke medicine, neurology, vascular surgery, vascular radiology, interventional neuroradiology, health economics, clinical trials and statistics, will oversee the management of the trial.

### Trial organisation

The study will be organised on behalf of the collaborators by the central office, located at the UCL Institute of Neurology in London. The office will be responsible for protocol design, data collection and management, and analysis of the results in consultation with the Steering and Data Monitoring Committees, but will consult with the collaborators at an annual meeting and at other times as necessary. Communication with investigators will also take place via a regular newsletter and the trial website.

### Payments to centres

While funding is available, the Lead Institution (UCL Institute of Neurology, London) will pay the participating centres a one-off payment of £100 for each patient randomised patient for whom correctly filled-out randomisation, technical data and one month follow-up forms have been received. Participating centres must invoice to the Lead Institution within 6-months of receipt of this revised protocol and thereafter 6 monthly in arrears. The Lead Centre may vary or terminate such payments in the future in accordance with budgetary needs and will inform the participating centre of such changes as they occur.

## **Indemnity**

ICSS is an academic trial performed as a collaborative effort for the benefit of patients, and is not performed for, or on behalf of an industry sponsor. The trial compares two existing forms of treatment currently used in many hospitals. The various devices approved for use in the trial are not investigational devices and are required by the protocol to be marketed and already in use in the carotid artery as recognised by the CE mark. Hence, the trial is not an industry sponsored test of a new treatment with unknown hazards. The trial protocol anticipates that some patients may be harmed inadvertently as a result of treatment in the trial. Indeed, the determination of the rate of these adverse outcome events is a major aim of the trial. However, we believe that the risks of these adverse events will be outweighed by the benefits of treatment in either arm of the trial. The trial protocol does not subject patients to hazards that the patient would not have encountered if they had received the trial treatments outside the context of the trial in routine practice. Hence, the organisers of the trial cannot take responsibility for any harm occurring to patients as a result of partaking in the trial. Individual investigators and hospitals are required to take responsibility for the occurrence of any adverse events in the same way as they would do if the treatments were performed outside the trial.

## **Website**

The trial website contains updated information about the trial together with downloadable copies of the protocol, trial data collection forms, newsletters and contact information. The names of the collaborating centres will be included on the website. The website address is [www.cavatas.com](http://www.cavatas.com) and all the pages are accessible to the public, patients and collaborators alike without a password. At present, the data collection forms cannot be completed on line.

## Definitions of Outcome Events

- **Transient ischaemic attack (TIA):** An acute disturbance of focal neurological function with symptoms lasting less than 24 hours attributed to cerebrovascular disease.
- **Transient monocular blindness (Amaurosis fugax):** Acute total or partial loss of vision in one eye with recovery within 24 hours attributed to vascular disease. This will be included as a variety of TIA.
- **Stroke:** An acute disturbance of focal neurological function with symptoms lasting more than 24 hours resulting from intracranial vascular disturbance. It must be established whether the cause is infarction or haemorrhage (primary intracranial or subarachnoid). Visual loss resulting from embolic or haemodynamic retinal ischaemia lasting more than 24 hours will be included within the category of stroke.
- **Myocardial Infarction:** Two of the following have to be documented: specific cardiac enzymes more than twice the upper limit of normal, a history of chest discomfort for at least half an hour, or the development of specific abnormalities (e.g. Q waves) on a standard 12 lead electrocardiogram.
- **Cranial Nerve Palsy:** weakness or sensory impairment in the distribution of one of the cranial nerves attributed to treatment.
- **Haematoma:** bleeding attributed to the treatment of carotid narrowing requiring new surgery, transfusion or prolonging hospital stay.
- **Disabling Outcome Events:** disability after stroke and cranial nerve palsy will be assessed using the Modified Rankin scale (defined below). Outcome events will be classified as disabling if the Rankin score is 3 or greater for more than 30 days after onset. The Rankin scale will be recorded at one and six months after treatment and then at annual follow up. Investigators will be asked to estimate the Rankin scale at one and six months after onset of new stroke when they see the patient more than 6 months after onset of stroke.
- **Recovered strokes:** in patients who make a full recovery from stroke or other outcome events, the duration from onset to full recovery will be recorded in days.
- **Modified Rankin Scale:** The following modified Rankin scale will be used to assess residual disability from stroke at randomisation to establish a baseline

level of disability and at every follow up visit to assess the severity of any subsequent stroke:

- 0 Asymptomatic.
- 1 Non-disabling symptoms which do not interfere with lifestyle.
- 2 Minor disability - symptoms which lead to some restriction of lifestyle but do not interfere with the patient's capacity to look after themselves.
- 3 Moderate disability – symptoms which significantly interfere with lifestyle or prevent totally independent existence, but able to walk without assistance.
- 4 Moderately severe disability – symptoms which clearly prevent independent existence, unable to walk without assistance, although the patient does not need constant attention day and night.
- 5 Severely disabled – totally dependent requiring constant attention day and night.
- 6 Dead.

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